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Perspetivas sobre o Presente e Futuro dos Registos Eletrónicos de Saúde em Portugal

Perspectives on the Present and Future of Electronic Health Records in Portugal

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Palavras-chave: Informática em Saúde Pública; Registos Eletrónicos de Saúde; Sistemas de Apoio a Decisões Clínicas
Keywords: Decision Support Systems, Clinical; Electronic Health Records; Public Health Informatics

O sistema de registo eletrónico de saúde (EHR – *Electronic Health Record*) revolucionou a organização dos sistemas de saúde e alavancou a desmaterialização de processos e o progresso digital.[1-3] Entre os vários benefícios previstos, o apoio à decisão e o acesso à informação destacaram-se desde cedo entre os campos mais promissores. Apesar das potencialidades previstas para os EHR aquando da sua implementação na década passada, as promessas destas tecnologias têm ficado aquém das expectativas. Investigações anteriores mostraram que muitas das expectativas dos profissionais de saúde em relação aos EHR não foram atendidas[4] e a perceção e satisfação da implementação e uso dos EHR ainda exige ajuste ao fluxo de trabalhos e à adoção de, entre outras, uma arquitetura e infraestrutura flexíveis.[5]

Com o objetivo de avaliar riscos e benefícios sobre a implementação do EHR, foi publicado em 2017 um estudo qualitativo no qual foi usada uma análise SWOT,[6] com a participação de administradores e elementos de equipas de gestão de informação de hospitais no Irão, já que a monitorização da implementação de EHR requer uma abordagem hierárquica e multidisciplinar. Mais recentemente, outro estudo reportou as dificuldades identificadas pelos profissionais de saúde durante o processo de codificação clínica por meio de EHR, designadamente a heterogeneidade e falta de informação, informação pouco clara, variabilidade na descrição da informação e ainda a falta de soluções e estratégia para resolução destes problemas.[7]

O presente estudo descreveu as perceções das partes interessadas e dos profissionais de saúde no âmbito dos EHR e comparou qualitativamente os resultados obtidos com os do trabalho publicado em 2017.

Os autores auscultaram alguns dos profissionais mais experientes na área, quer do ecossistema público ou privado, sobre os panoramas atual e futuro dos EHR em seis dimensões e replicou-se a análise SWOT[6] para um público abrangente. A amostra incluiu 67 participantes na fase de discussão e 36 na análise SWOT. Utilizou-se uma amostragem por conveniência e em bola de neve. O perfil do participante foi variado e definido no momento de preenchimento do formulário de resposta fechada. Contou-se com 25% de cientistas de dados, 25% de participantes da área da saúde, 22,2% de participantes médicos, 19,4% de participantes da área de sistemas e tecnologias de informação e 2,8% de participantes gestores. A média de anos de experiência no campo da informática médica foi de 6,33 anos no grupo de não médicos e de 7,08 anos no grupo de médicos. A divulgação do *workshop* foi realizada via *e-mail* e através de redes sociais nacionais e internacionais. A recolha de dados englobou três fases: (i) revisão preliminar da literatura para identificar tópicos e secções de discussão, (ii) discussão em grupo até saturação e consenso do grupo e (iii) preenchimento individual de um formulário eletrónico *online*. Durante a primeira fase de revisão de literatura desenvolveram-se tópicos que serviram para a discussão em grupo na segunda fase. A discussão em grupo ocorreu até se obter um consenso e exaustão do tópico e ocorreu em seis dimensões prioritárias previamente definidas (inserção de dados, armazenamento, visualização, comunicação/interoperabilidade, suporte à decisão, outro) para as quais foram discutidos sequencialmente os aspetos característicos do passado e do presente *versus* o futuro dos EHRs. Os investigadores identificaram duplicados e sinónimos e resumiram conceitos únicos que caracterizavam independentemente as dimensões em estudo. Para a terceira fase, e tendo por base o estudo de Shahmoradi L *et al*,[6] o formulário conteve duas secções, designadamente, (i) informação do perfil do participante; e (ii) 30 questões para análise SWOT, tendo por base uma escala de 5 pontos (pontuação 1 a 5, com crescente nível de importância). Calculou-se a média e o desvio padrão para cada pergunta em ambos os grupos de participantes médicos e não médicos e utilizou-se o teste *t de Student* de forma a comparar a média de respostas para cada item da análise SWOT (significância de alfa de 5%). Posteriormente, comparou-se externamente de forma descritiva os resultados obtidos com

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Tabela 1 – Resultados da discussão de grupo

Secção	Características previamente identificadas	Características adicionadas durante a discussão
Inserção dados		
P	Narrativa e alguns dados estruturados Pequenos desenhos ou esquemas Abundância de códigos / terminologias locais Dispositivo de entrada: teclado + rato	Inserção de dados não ajustada ao percurso clínico Dificuldade de utilização de dados para fins de investigação Reduzida reutilização de dados, com necessidade de duplicação Descuido na proteção a acessos indevidos
F	Reconhecimento de voz e NPL Padrões internacionais para terminologias e ontologias Modelos de importação (*open*EHR, FHIR, eCRFs) Promoção da qualidade dos dados Melhoria no design/interface usuário Uso de dispositivos pessoais para aceder EHR (BYOD)	Inserção por *wearable devices* (e outras IoT) Informação recolhida pelo utente (incluindo PROMS) Integração do hardware nos processos de trabalho Integração com exames complementares de diagnóstico (paradigma Telemedicina; anexar exames / imagens - ex: dermatologia) Modelos de dados ER *versus* modelos EAV para dados específicos e *forms* customizáveis por cada unidade/profissional.
Armazenamento de dados		
P	Bases de dados relacionais Problemas de qualidade de dados Falta de padrões Falta de compreensão da modelagem de dados clínicos	Falta de API's Ausência de separação entre o modelo de conhecimento e o modelo de informação Ausência de metadados
F	Baseado em documentos Padronizado: *open*EHR, FHIR, CDISC Armazenamento de dados do nascimento à morte Armazenamento de dados clínicos + imagem + sinais + genéticos	Bases de dados federadas Registo de acessos às bases de dados *Cloud-based* (privada e publica) Comunicação entre quem a preenche, fórmula e a compõe
Informação/visualização de dados		
P	Relatórios, formulários de entrada para ler Incapacidade do clínico de descrever completamente a história clínica do paciente nos EHRs Barreiras à inovação	Inserção e visualização de dados agregada Visualização baseada 'em papel' (estática)
F	Dados resumidos Linhas do tempo Tradução embutida Maior acesso e controle do paciente	Realidade aumentada Suporte de informação para simulação clínica - diagnóstico e terapêutica Necessidades de informação devem ser orientadas ao contexto e aos utilizadores (*user-centric*) Ajustar literacia da informação ao utilizador *Scores* e/ou alerta de risco; *outliers*; dados em tempo real Suporte inter e intrainstituições para vigilância epidemiológica Hierarquização da informação baseada em contexto *Dashboard* criado pelo utilizador (profissional de saúde) Grau de adesão/afastamento das decisões clínicas aos protocolos terapêuticos
Comunicação/interoperabilidade		
P	Diferenças na semântica e dicionários de dados Falta de APIs de fornecedores Silos isolados	*Vendor lock* dependência de fornecedor
F	Fluxos de controle de inteligência artificial Padronizações *Plug-in* novos APPs no EHR com poucas personalizações Incorporação de melhores medidas de segurança Integração de muitas fontes de dados diferentes (imagem, genética, social, *fitness*, bem-estar, ...)	*Blockchain* na Saúde: validação e partilha *Plug-ins* utilizando metadados para integração automática Regulamentação (exemplo: farmacovigilância) Utilizar modelos clínicos de dados abertos Uso de e apoio a soluções *open-source* Definição nacional de terminologias Comunicação entre sistemas
Suporte à decisão		
P	Escasso/inexistente Alertas Simples Não certificado	Ausência de *standards* de simbologias para alertas
F	Aprendizagem com a nova utilização Incorpora facilmente novos conhecimentos Utilização de todo o espectro de dados Certificado Monitorização e aprendizagem com eventos adversos Diagnóstico de computador Apoio à Medicina de Precisão	Grau de adesão/afastamento das decisões clínicas aos protocolos terapêuticos Modelação de orientações clínicas de forma que sejam computáveis Governança, gestão de risco e conformidade Questões éticas e de confiança por parte dos profissionais e dos doentes
Outras		
P	-	-
F	Componentes de conexão Personalização mais fácil por médicos	-

API: interface de programação de aplicativos; APPs: aplicativos; BYOD: traga o seu próprio dispositivo; CDISC: Consórcio de Padrões de Intercâmbio de Dados Clínicos; EAV: modelo entidade-atributo-valor; eCRF: formulário eletrônico de relatório de caso; ERV: modelo entidade-relacionamento; FHIR: recursos de interoperabilidade rápida em saúde; F: futuro; IoT: internet das coisas; NPL: processamento de linguagem natural; openEHR: especificação aberta do padrão de informática em saúde que descreve a gestão e armazenamento, recuperação e troca de dados de saúde em registos eletrônicos de saúde; P: passado e presente; PROMS: métricas de resultados relatadas pelo paciente.

os resultados do estudo de 2017.[7]

A Tabela 1 agrega a informação da discussão de grupo dos diferentes tópicos propostos. De uma forma geral, em todas as secções foram propostas melhorias e adicionada informação relevante não contemplada anteriormente, realçando-se nomeadamente a ausência de referências de simbologias para alertas, metadados ou bases federadas, e a necessidade de (i) informação que deve ser orientada de acordo com o contexto e os utilizadores (*user-centric*) e (ii) governança, gestão de risco e conformidade.

Na Tabela 2 estão presentes os resultados da análise SWOT. Genericamente, não se encontraram diferenças estatisticamente significativas em nenhum grupo e os resultados são consistentes quer na comparação interna entre médicos e não médicos quer na comparação externa entre estudos. O ponto forte com maior relevância em todos os grupos foi a "Facilidade de acesso à informação e em tempo útil". Internamente, a fraqueza mais preocupante foi "Ser demorado e difícil estabelecer a ligação da informação contida em sistemas legados à de novos sistemas", não coincidente com o estudo de comparação. A oportunidade de "Partilha de informação entre prestadores de cuidados de saúde e melhor gestão de informação" foi a mais valorizada em todos os grupos, exceto no grupo de profissionais de informática médica. Quanto às ameaças, o item "Falta de planeamento estratégico na área dos EHR" foi o mais cotado, exceto para o grupo de médicos e para o grupo de profissionais de informática médica, que valorizaram respetivamente a "Ausência de um vocabulário padronizado a nível nacional para o estabelecimento de EHRs" e "Resistência dos profissionais de saúde na adoção e uso dos EHR". Não se verificaram diferenças estatisticamente significativas entre os grupos.

Este estudo permitiu traçar o panorama das potencialidades e constrangimentos no âmbito do passado e futuro dos EHRs.

Adicionalmente, o nosso grupo avaliou quantitativamente, através de uma análise SWOT, a importância de vários *itens* característicos dos EHRs, comparando os resultados obtidos num grupo de médicos com um de não médicos, ambos experientes na área da informática médica e com especial interesse nas áreas de estudo de Ciência de Dados de Saúde e Sistemas e Tecnologias de Informação. Posteriormente, os resultados deste trabalho foram qualitativamente comparados com os resultados do estudo realizado em 2017.[6] O levantamento de necessidades e aplicabilidade das tecnologias continua a exigir que se premeie primariamente a voz dos utilizadores. O *design* do *workshop* foi pioneiro na utilização do formato *webinar*, permitindo quer a aproximação entre os participantes e apresentadores quer o acréscimo de valor, de forma bilateral, à estrutura da apresentação. Paralelamente, o presente estudo revelou, em termos gerais, coerência com os achados do estudo de Shahmoradi L *et al,*[6] apesar das diferenças nas amostras selecionadas (médicos e não médicos *versus* gestores e profissionais de informática médica), o que reforça a consistência dos resultados obtidos.

O nosso estudo apresenta limitações, tais como questões culturais e geográficas não consideradas, ou o impacto do contexto pandémico na perceção dos participantes. A representatividade das partes interessadas e a adesão ao evento pode ter sido afetada pela limitada promoção do *workshop* a grupos restritos e pelos constrangimentos de horário que muitos profissionais de saúde (especialmente médicos) sentem para participar em eventos desta natureza.

Em suma, quer pela ausência de um vocabulário padronizado, quer pela falta de planeamento estratégico, os EHRs parecem estar aquém das expectativas, designadamente como um sistema com a capacidade de trocar eficientemente e integrar dados e informações, auxiliando a tomada de decisão e promovendo a comunicação e colaboração entre partes interessadas na prestação de cuidados de saúde. Este estudo tem o potencial de orientar a definição de eixos estratégicos para decisores e gestores, ao auxiliar na priorização de futuros investimentos e intervenções, e de delinear *roadmaps* para a operacionalização dos mesmos. Futuras investigações devem considerar o potencial dos *webinars* para reunir evidência e alargar estas discussões a amostras mais representativas do ecossistema.

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CONTRIBUTO DOS AUTORES

DP: Concepção e redação do artigo. Recolha, análise e interpretação dos dados.

SF: Concepção do artigo. Recolha, análise e interpretação dos dados. Aprovação da versão final do manuscrito.

PP: Conceção do estudo, revisão crítica e aprovação da versão final do manuscrito.

RCC: Conceção do estudo, recolha de dados, revisão crítica e aprovação da versão final do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial actualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

Tabela 2 – Análise SWOT

	Comparação interna dos dados colhidos durante o *webinar*				Comparação externa com os dados do estudo realizado previamente por Shahmoradi L *et al*[6]	
	Total de participantes	Médicos	Não médicos	Teste *T Student* (*p-value*)**	Gestores	Profissionais de informática médica
	Média (desvio padrão)				Média	
Forças*						
Facilidade de acesso à informação e em tempo útil	**3,64** (1,16)	**3,29 (1,03)**	**3,72** (1,17)	0,88 (0,38)	**3,75**	**2,32**
Precisão no registo dos serviços prestados	3,28 (0,96)	2,86 (0,64)	3,38 (1,0)	-0,72 (0,47)	3,19	2,2
Redução de testes duplicados incluindo testes laboratoriais	3,22 (1,18)	2,29 (1,03)	3,45 (1,1)	2,47 (0,02)	3,38	2,17
Capacidade de informatizar a análise e interpretação de informação	3,22 (1,27)	2,57 (1,29)	3,38 (1,22)	2,14 (0,04)	3,25	2,1
Troca eletrônica de informação e participação na prestação de cuidados	3,08 (1,14)	2,29 (0,88)	3,28 (1,11)	-0,14 (0,89)	3,31	2,17
Prevenção de erros clínicos	3,06 (1,05)	2,43 (0,73)	3,21 (1,06)	1,28 (0,21)	2,94	1,88
Aumento da velocidade da prestação de serviços	2,94 (1,1)	3,00 (1,31)	2,93 (1,05)	1,51 (0,14)	3,13	2,27
Armazenamento de informação com baixo volume	2,81 (0,78)	3,00 (0,93)	2,76 (0,73)	1,78 (0,08)	3,38	2,2
Fraquezas*						
Ser demorado e difícil estabelecer a ligação da informação contida em sistemas legados à de novos sistemas	**3,89** (1,33)	**4,14** (1,46)	**3,83** (1,29)	0,75 (0,46)	2,50	1,85
Falta de equipamento necessário para a implementação adequada dos EHR	3,56 (1,04)	3,29 (0,88)	3,62 (1,06)	-0,55 (0,59)	**2,81**	1,85
Aumento da carga de trabalho dos profissionais de saúde	3,08 (1,21)	3,29 (1,28)	3,03 (1,19)	-0,48 (0,63)	2,69	1,63
Criação de problemas de digitação pelos administrativos	2,83 (1,07)	3,14 (0,99)	2,76 (1,07)	-0,84 (0,41)	2,50	**1,90**
Ausência de lucro rápido	2,78 (1,25)	2,71 (1,28)	2,79 (1,24)	0,15 (0,89)	2,50	1,85
Imposição de demasiado controlo e disciplina aos funcionários	2,67 (1,15)	2,43 (0,9)	2,72 (1,20)	0,59 (0,56)	2,06	1,83
Colocando empregos em risco pela implementação de EHR	1,89 (1,22)	1,86 (0,83)	1,90 (1,30)	0,07 (0,94)	1,75	1,63
Oportunidades*						
Partilha de informação entre prestadores de cuidados de saúde e melhor gestão de informação	**4,50 (0,69)**	**4,29 (1,03)**	**4,55 (0,56)**	-0,03 (0,98)	**3,25**	2,20
Acesso a uma variedade de estatísticas de saúde	4,28 (0,80)	**4,29 (1,03)**	4,28 (0,74)	-1,60 (0,12)	3,19	**2,27**
Coordenação semântica e comunicação entre partes internas e externas	4,17 (0,87)	4,14 (1,12)	4,17 (0,79)	0,76 (0,45)	2,56	2,07
Garantia de integridade de todo o sistema	4,08 (0,86)	3,86 (1,25)	4,14 (0,73)	0,08 (0,94)	2,50	2,15
Uso como fonte principal de formação entre médicos e prestadores de serviços públicos	3,89 (0,87)	4,00 (0,76)	3,86 (0,90)	-1,54 (0,13)	**3,25**	2,20
Aplicado como documento legal sobre o tipo de serviços prestados	3,78 (0,97)	**4,29 (0,70)**	3,66 (0,99)	-0,18 (0,86)	2,06	1,93
Registos de forma precisa dos serviços prestados com intuito de realizar reembolsos de impostos individuais	3,72 (1,04)	**4,29 (0,70)**	3,59 (1,07)	-0,03 (0,98)	2,56	2,20
Ameaças*						
Falta de planeamento estratégico na área dos EHR	**4,08 (0,95)**	4,14 (0,64)	**4,07 (1,01)**	-0,71 (0,48)	**3,38**	1,98
Acesso não autorizado às informações do paciente	3,97 (1,04)	4,00 (0,93)	3,97 (1,07)	1,24 (0,22)	2,69	1,78
Ausência de um vocabulário padronizado a nível nacional para o estabelecimento de EHRs	3,94 (1,00)	**4,43 (0,49)**	3,83 (1,05)	-0,96 (0,34)	2,50	2,05
Falta de fundos para conceção, implementação e uso de EHR	3,92 (1,11)	4,29 (0,70)	3,83 (1,18)	-1,47 (0,15)	2,94	1,85
Falta de recursos humanos especializados	3,81 (0,97)	4,29 (0,70)	3,69 (0,99)	-0,08 (0,94)	2,69	1,93
Falta de consciencialização dos profissionais de saúde sobre os benefícios dos EHR	3,81 (1,05)	4,14 (0,64)	3,72 (1,11)	-0,93 (0,36)	2,75	2,05
Problemas relacionados com programação e desenvolvimento de software de acordo com as necessidades	3,58 (1,11)	3,86 (0,99)	3,52 (1,13)	-1,43 (0,16)	3,13	2,02
Resistência dos profissionais de saúde na adoção e uso dos EHR	3,58 (1,04)	3,14 (0,99)	3,69 (1,02)	-0,71 (0,48)	2,94	**2,20**

* Ordenados de acordo com o estudo realizado previamente por Shahmoradi L *et al.*[6].

** Resultados da análise estatística de comparação de médias entre grupo de médicos e não médicos para cada um dos itens da análise SWOT.

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Association between Body Mass Index and Gestational Weight Gain with Obstetric and Neonatal Complications in Pregnant Women with Gestational Diabetes

Índice de Massa Corporal e Ganho Ponderal Associado a Complicações Obstétricas e Neonatais na Diabetes Gestacional

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ABSTRACT

Introduction: Gestational diabetes is a condition that predisposes to complications during pregnancy and to the newborn. The aim of this study was to assess the association between body mass index and gestational weight gain and obstetric and neonatal complications in pregnant women with gestational diabetes.

Material and Methods: Retrospective cohort study involving 13 467 singleton pregnancies with gestational diabetes, diagnosed between 2014 and 2018, in Portugal. This sample was distributed according to the World Health Organization body mass index categories (underweight, normal, overweight, or obese) and according to the Institute of Medicine guidelines for gestational weight gain groups (adequate, insufficient, or excessive). Binomial and multinomial logistic regression models were applied to determine risk factors for complications in pregnant women with gestational diabetes. Data analysis was performed with SPSS version 25.

Results: Pregestational overweight and obesity were associated with an increased risk of maternal morbidity (aOR: 1.31; aOR: 2.42), gestational hypertension (aOR: 1.56; aOR: 2.79) and caesarean section (aOR: 1.22; aOR: 1.77) whilst reducing the risk for small for gestational age [aOR: 0.73; aOR: 0.64 (Fenton chart); aOR: 0.69; aOR: 0.66 (Portuguese chart)]. Obesity alone was associated with increased preeclampsia events (aOR: 3.05), respiratory distress syndrome (aOR: 1.69), admission to neonatal intensive care unit (aOR: 1.54), macrosomia (aOR: 2.18), and large for gestational age [aOR: 2.03 (Fenton); aOR: 1.87 (Portuguese)] and decreased risk of low birthweight newborns (aOR: 0.62). Insufficient gestational weight gain was associated with a decreased risk of gestational hypertension (aOR: 0.69), preeclampsia (aOR: 0.44), Caesarean section (aOR: 0.81) and large for gestational age [aOR: 0.74 (Portuguese)] and increased risk of low birthweight (aOR: 1.36) and small for gestational age [aOR: 1.40 (Fenton)]. Excessive gestational weight gain was associated with increased risk of gestational hypertension (aOR: 1.53), hydramnios (aOR: 2.05), macrosomia (aOR: 2.02), and large for gestational age [aOR: 1.94 (Fenton); aOR: 1.92 (Portuguese)].

Conclusion: Pregestational overweight and obesity, as well as excessive weight gain are associated with an increased risk of certain obstetric and neonatal complications. It is essential to have an appropriate pre-conceptional surveillance and a close follow-up during pregnancy in order to reduce the associated risks and the probable predisposition of these newborns to severe outcomes.

Keywords: Body Mass Index; Gestational Diabetes; Gestational Weight Gain; Infant, Newborn; Postpartum Period; Pregnancy Complications

RESUMO

Introdução: A diabetes gestacional é uma condição que predispõe a complicações maternas durante a gravidez e ao recém-nascido. Este estudo visa analisar o impacto do índice de massa corporal e do ganho ponderal durante a gravidez na ocorrência de complicações obstétricas e neonatais das diabéticas gestacionais.

Material e Métodos: Estudo retrospetivo de coorte que envolveu 13 467 grávidas com gestações únicas e diagnosticadas com diabetes gestacional, entre 2014 e 2018, em Portugal. A amostra foi distribuída de acordo com os critérios da Organização Mundial da Saúde para as categorias de índice de massa corporal (baixo peso, normal, excesso de peso e obesidade) e de acordo com as guidelines do Instituto de Medicina Americano para ganho ponderal gestacional (adequado, insuficiente ou excessivo). Foram usados modelos de regressão binomial e multinomial para determinar os fatores de risco de complicações na diabetes gestacional. A análise estatística foi realizada a partir do SPSS versão 25.

Resultados: Excesso ponderal e obesidade pré-gestacionais aumentaram o risco de morbilidade maternal (aOR: 1,31 e aOR: 2,42), hipertensão gestacional (aOR: 1,56 e aOR: 2,79) e realização de cesarianas (aOR: 1,22 e aOR: 1,77), contudo diminuíram o risco para recém-nascidos pequenos para idade gestacional [aOR: 0,73; aOR: 0,64 (curvas Fenton) e aOR: 0,69; aOR: 0,66 (curvas portuguesas)]. A obesidade esteve associada a um risco aumentado de eventos de pré-eclampsia (aOR: 3,05), síndrome de dificuldade respiratória neonatal (aOR: 1,69), internamentos em cuidados intensivos neonatais (aOR: 1,54), macrossomia (aOR: 2,18) e grandes para idade gestacional [aOR: 2,03 (Fenton) e aOR: 1,87 (portuguesas)] e foi associada a menor risco de recém-nascidos com baixo peso à nascença (aOR: 0,62). O ganho ponderal insuficiente estava associado a um risco mais baixo de hipertensão gestacional (aOR: 0,69), pré-eclampsia (aOR: 0,44), cesarianas (aOR: 0,81) e grandes para idade gestacional (aOR: 0,74 [portuguesas]) e esteve associado a maior risco de baixo peso à nascença (aOR: 1,36) e pequeno para idade gestacional [aOR: 1,40 (Fenton)]. O ganho ponderal excessivo teve maior associação com hipertensão gestacional (aOR: 1,53), hidrâmnios (aOR: 2,05), macrossomia (aOR: 2,02) e grandes para idade gestacional [aOR: 1,94 (Fenton) e aOR: 1,92 (portuguesas)].

Conclusão: Tanto o excesso de peso e obesidade pré-gestacional, como o ganho ponderal excessivo estiveram associados a um risco aumentado de determinadas complicações obstétricas e neonatais. É fundamental apresentar uma vigilância na preconceção apropriada e um acompanhamento apertado da gravidez de modo a reduzir os riscos associados e a predisposição destes

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recém-nascidos a patologias diversas.
Palavras-chave: Complicações na Gravidez; Diabetes Gestacional; Ganho de Peso na Gestação; Índice de Massa Corporal; Período Pós-Parto; Recém-Nascido

INTRODUCTION

During pregnancy, physiological changes occur that predispose pregnant women to maternal complications and increase the risk of neonatal morbidity and mortality. Gestational diabetes (GD) is a metabolic change diagnosed during gestation which causes intolerance to carbohydrates due to pancreatic insufficiency and insulin resistance induced by the secretion of placental diabetogenic hormones.[1,2]

The prevalence of GD has been increasing worldwide and in Portugal it is about 6.5% to 7.5%.[3] This increase may be explained by the stricter diagnostic criteria established in 2011 by the Portuguese Directorate-General of Health, the Direção Geral de Saúde (DGS), and by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), associated with an increase in the incidence of obesity within the Portuguese population.[4]

The anthropometric characteristics such as pregestational body mass index (BMI) and total weight gain at the end of pregnancy may foresee the pregnancy pathway and the neonatal outcomes. They may increase the probability and severity of certain complications during pregnancy, during delivery and to the newborn.[5-7] Many studies, mostly carried out in normal pregnancies and a few in gestational diabetes, have shown the association of pregestational BMI and gestational weight gain with complications such as gestational hypertension,[8,12,13,16-20] preeclampsia,[14] caesarean delivery,[8,13,14,22] macrosomia,[9-11,15-20,22] large for gestational age (LGA),[9,10,12,14-22] admission into a neonatal intensive care unit,[13] and many other outcomes.

There is currently lack of data about gestational diabetes in Portugal, and hospital follow-up is still in its early phase, with no streamlined guidelines for pregnant patients with diabetes.

Therefore, the goal of this study is to evaluate the association between pregestational BMI and the final gestational weight gain (GWG), and the occurrence of maternal and neonatal complications in GD pregnant women and their newborns, in Portugal. Additionally, we will also evaluate the effect of previous BMI and GWG on postpartum reclassification of GD patients.[23-26]

MATERIAL AND METHODS

We performed an observational cohort study following the STROBE reporting guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).

Ethics committee approval was not required because this study involved the analysis of a national dataset obtained from the Portuguese Diabetes Society where the data are properly anonymized and informed consent was obtained at the time of original data collection.

We analyzed retrospective data from pregnant women diagnosed with GD or with previous/*de novo* diabetes mellitus followed-up in public healthcare institutions between January 2014 and December 2018. The data used was collected from the national registry of GD that is under the responsibility of the Diabetes and Pregnancy Study Groups implemented by the Portuguese Diabetes Society in which some of the maternity health centers and hospitals in Portugal are represented. The data was collected by hospital volunteers via analysis of electronic health records and directly during patient interviews.

Participants' selection criteria

For this study, we analyzed data from pregnant patients followed in hospital outpatient care for chronic or *de novo* glucose metabolism anomaly, between 2014 and 2018. The diagnosis was based on the DGS-IADPSG criteria, through fasting glucose ≥ 92 mg/dL or through oral glucose tolerance test (OGTT) taken between week 24 and 28 (0' ≥ 92 mg/dL and/or 60' ≥ 180 mg/dL and/or 120' ≥ 153 mg/dL). A total of 17 959 pregnant women were identified.

We excluded underaged pregnant patients (under 18 years of age), patients with no data on BMI and GWG available for consultation (missing data), previous or *de novo* diagnosis of diabetes mellitus [fasting glucose values or OGTT 0' ≥ 126 mg/dL or occasional glucose values (OGTT 60' and 120') ≥ 200 mg/dL], and multifetal pregnancies. Additionally, we decided to exclude the participants that demonstrated more than three standard deviations from the GWG mean (10.6 ± 5.9 kg, and therefore participants that showed GWG above 28.3 kg and below -7.1 kg were excluded). Hence, our sample consisted in the information of 13 467 pregnant women and their corresponding newborns (Fig. 1).

Analysis of variables and primary and secondary outcomes

The following participant information were analyzed: age (years-old), academic degree (none or unknown, primary until fourth or sixth grade, primary until ninth grade, secondary until twelfth grade and higher education), calculated BMI from pregestational weight and height, first-degree family history of diabetes mellitus, number of previous abortions/deliveries and gestations, previous GD/macrosomia, diagnosis made from fasting glucose or OGTT, gestational week of diagnosis, week of first hospital appointment, number of weeks from diagnosis until first appointment, GWG (kg), treatment used [diet and exercise (non-pharmacological), only insulin, only oral hypoglycaemic drug (OHD) or insulin and OHD], daily insulin units, and daily dosage of OHD (metformin) in milligrams.

The calculated pregestational BMI was categorized according to the World Health Organization (WHO) criteria as underweight (< 18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (≥ 30 kg/m^2).

GWG was estimated from the difference between weight at delivery or at the last appointment before

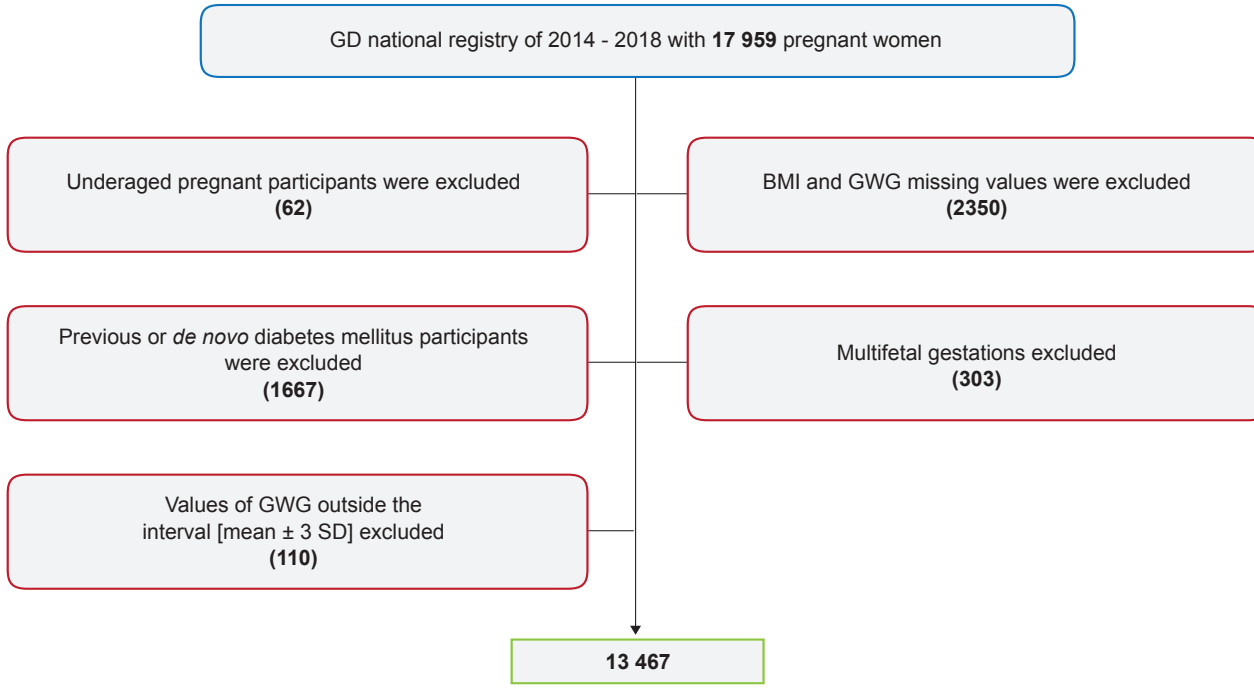

Figure 1 – Flowchart of the final sample

delivery, and pregestational weight. It was then categorized into adequate, insufficient, and excessive as recommended by the Institute of Medicine (IOM), within each BMI category. Therefore, GWG was considered adequate if it was within the range of 12.5 – 18 kg for underweight, 11.5 – 16 kg for normal weight, 7 – 11.5 kg overweight and 5 – 9 kg for obese, and insufficient or excessive when the values were, respectively, below or above the intervals indicated for each category.

We also analyzed delivery information: week of delivery, type of delivery (eutocia or dystocia, Caesarean delivery), type of Caesarean delivery (urgent or elective), and newborn characteristics, like weight (g).

As for study outcomes, we evaluated the occurrence of maternal and neonatal complications and reclassification at six to eight weeks postpartum regarding the pregestational BMI and GWG of the GD population in Portugal. Pregnancy complications included maternal morbidity that comprised at least one of the following secondary outcomes: abortion, gestational arterial hypertension (gHT), preeclampsia, hydramnios, fetal death and Caesarean delivery. Another primary outcome was the development of neonatal complications, such as neonatal morbidity or mortality. Secondary outcomes to neonatal morbidity were: neonatal hypoglycaemia, hyperbilirubinemia, respiratory distress syndrome (RDS), admission to the neonatal intensive care unit (NICU), premature (delivery at < 37 gestational weeks), large for gestational age (LGA; weight above the 90th percentile), small for gestational age (SGA; weight below the 10th percentile), macrosomia (birthweight ≥ 4000 g), low birthweight (< 2500 g), trauma at delivery, and congenital abnormalities. LGA and SGA were characterized according to the Fenton charts and the Portuguese population adapted charts. Regarding postnatal reclassification, we evaluated the impact of pregestational BMI and GWG group on the development of impaired fasting glucose, impaired glucose tolerance, and postnatal diabetes mellitus.

Statistical analysis

Statistical analysis was performed through Statistical Package for Social Science (SPSS®) software, 25.0 version. Continuous variables were defined by mean and standard deviations (SD), after checking for symmetry of distributions by observing histograms. Medians and percentiles P25 and P75 were presented otherwise. Considering our sample size, we checked histograms, symmetry, and kurtosis to assess normal distribution of continuous variables. Categorical variables were defined by total number and frequency (%). When needed, continuous variables were transformed into dichotomous categorical variables, like prematurity and macrosomia.

As for the variable inferential analysis, we used non-parametric Kruskal-Wallis and Mann–Whitney U tests when it involved one continuous non-normal distributed variable and a categorical variable. For categorical variables, we used the χ^2 test or the Fisher's exact test (dichotomic variables and ≥ 20% cells with expected count < 5).

To assess associations, we used binomial and multinomial logistic regression to obtain crude and adjusted odds ratios (aOR) with the confidence intervals at 95% (CI 95%). The association of the main variables (BMI category and GWG group) was adjusted for maternal age, number of previous abortions/deliveries, first-degree family history of diabetes mellitus, previous macrosomia, diagnosis through

fasting glucose, number of weeks between diagnosis and first hospital appointment, week of delivery, and treatment used for GD (diet and exercise versus insulin versus OHD). These variables were selected after analysis of univariable association between each of the covariates and each of the outcomes (dependent variables). At the end, only the ones with statistically significant association were selected (*p* value < 0.05). After selection, we applied the forward likelihood ratio for the binomial logistic regression and forward stepwise for the multinomial logistic regression that calculated the aOR after checking the interaction of the chosen covariates.

All tests with statistical significance were bilateral, considering a *p* value of < 0.05 as statistically significant.

RESULTS

Sample characterization

The characteristics of our sample are shown in Table 1.

Regarding BMI, 41.2% (n = 5550) presented a normal pregestational BMI, 1.9% (n = 261) were underweight, and almost 57% (n = 7656) were overweight to obese participants.

As for GWG, only 32.5% (n = 4372) of the participants had adequate gain according to IOM criteria, whilst 38.9% (n = 5245) had insufficient gain and 28.6% (n = 3850) had excessive GWG.

It is worthy of note that overweight and obese participants had higher percentage of first-degree family history of diabetes mellitus (46.8%, n = 1865 and 49.4%, n = 1725, respectively), and history of previous GD (19.5%, n = 546 and 21.3%, n = 554, respectively) and macrosomia (7.6%, n = 212 and 11%, n = 283, respectively). These participants also showed higher incidence of excessive GWG (38.6%, n = 1569 and 36.2%, n = 1302, respectively) and need for pharmacological therapy for the treatment of GD (42.6%, n = 1702 and 56%, n = 1982, respectively), as well as higher daily dosage of insulin (mean of 20.6 ± 16.9 U/day and 24.2 ± 22.6 U/day, respectively) and/or OHD (mean of 1387.4 ± 633.6 mg/day and 1510.6 ± 736.6 mg/day, respectively) compared with normal or underweight groups [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

Diagnosis and management of gestational diabetes

Almost half of the patients were diagnosed with GD through fasting glucose (46.9%, n = 6320), whilst the rest were diagnosed through OGTT (51.6%, n = 6945).

As for the treatment used in GD, 59.4% (n = 7856) of the participants achieved glycemic control (after analyzing fasting and postprandial glycemic records), with only diet and physical activity, whilst the rest required OHD and/or insulin therapy.

Pregnant women with excessive GWG required a higher daily dosage of insulin (mean of 23.3 ± 22.9 U/day) in order to control GD compared to those with adequate (mean of 20.3 ± 15.6 U/day) or insufficient gain (mean of 19 ± 16.5 U/day) [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

The distribution of the sample, according to its characteristics, in each BMI category and GWG group, as well as the inferential analysis, can be ascertained in Appendix 1, as Tables 1 and 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf).

Maternal and neonatal complications

Previously overweight or obese participants and patients with excessive GWG had higher number of deliveries by caesarean section, especially as urgent deliveries [Appendix 1, Tables 3 and 4 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

As for the newborns, their weight increased with increasing BMI categories. Excessive GWG was also associated with higher birthweight [mean of 3318 ± 493.3 g in Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

The inferential analysis of BMI categories and obstetric complications showed that global maternal morbidity, especially preeclampsia, gHT, and caesarean section were differently affected within the BMI categories, with statistical significance (Table 2). We found that pregestational overweight and obesity were associated with an increased risk of maternal morbidity (aOR: 1.31; CI 95%: 1.06 - 1.61 and aOR: 2.42; CI 95%: 1.99 - 2.94, respectively), gHT (aOR: 1.56; CI 95%: 1.05 - 2.31 and aOR: 2.79; CI 95%: 1.94 - 4.02, respectively), and caesarean section (aOR: 1.22; CI 95%: 1.02 - 1.46 and aOR: 1.77; CI 95%: 1.48 - 2.11, respectively). There was only a positive association between pregestational obese participants and risk for preeclampsia, with statistical significance (aOR: 3.05; CI 95%: 1.93 - 4.82) (Table 4).

When analyzing GWG, all maternal complications demonstrated statistically significant differences between the various groups, apart from fetal mortality (Table 3). However, the logistic regression analysis showed that insufficient GWG was associated with decreased occurrence of gHT (aOR: 0.69; CI 95%: 0.48 - 0.98), preeclampsia (aOR: 0.44; CI 95%: 0.28 - 0.68), and caesarean section (aOR: 0.81; CI 95%: 0.69 - 0.96). On the other hand, an excessive GWG increased the risk of gestational hypertension (aOR: 1.53; CI 95%: 1.11 - 2.12) and hydramnios (aOR: 2.05; CI 95%: 1.19 - 3.53) (Table 5).

Regarding neonatal complications, neonatal morbidity such as hyperbilirubinemia, prematurity, macrosomia or low birthweight, LGA or SGA, and trauma during delivery, there were statistically significant differences between the BMI groups (Table 2). Participants with pregestational obesity showed higher probability of their newborns developing RDS (aOR: 1.69; CI 95%: 1.14 - 2.51), being admitted in NICU (aOR: 1.54; CI 95%: 1.19 - 1.99), having macrosomia

Table 1 – Sample characteristics: mothers and their newborns (n = 13 467)

Characteristics	*p* value
Maternal age, mean ± SD (years old)	33.3 ± 5.3
median (P25; P75)	34.0 (30; 37)
Maternal academic qualification, n (%)	11 608 (86.2%)
None or unknown	69 (0.6%)
Primary (4th - 6th grade)	947 (8.2%)
Primary (9th grade)	2648 (22.8%)
High school (12th grade)	3983 (34.3%)
Higher education	3961 (34.1%)
Maternal BMI, mean ± SD (kg/m^2)	27.0 ± 5.8
median (P25; P75)	25.9 (22.7; 30.4)
Underweight (< 18.5), n (%)	261 (1.9%)
Normal (18.5 - 24.9), n (%)	5550 (41.2%)
Overweight (25 - 29.9), n (%)	4064 (30.2%)
Obese (≥ 30), n (%)	3592 (26.7%)
1st degree familial diabetes mellitus, n (%)	13 195 (98.0%)
Yes	5798 (43.9%)
Number of previous abortions, mean ± SD (units)	0.4 ± 0.7
median (P25; P75)	0 (0; 1)
Number of previous deliveries, mean ± SD (units)	0.8 ± 0.9
median (P25; P75)	1 (0; 1)
Number of gestations, mean ± SD (units)	2.2 ± 1.2
median (P25; P75)	2 (1; 3)
Previous gestacional diabetes, n (%)	8822 (65.5%)
Yes	1659 (18.8%)
Previous macrosomia, n (%)	8746 (64.9%)
Yes	668 (7.6%)
Fasting glucose diagnosis, n (%)	6320 (46.9%)
Mean ± SD (mg/dL); median (P25; P75)	96.7 ± 5.4; 95 (93; 98)
Diagnosis by OGTT, n (%)	6945 (51.6%)
OGTT 0' mean ± SD (mg/dL); median (P25; P75)	82.3 ± 11.0; 81 (75; 92)
OGTT 60' mean ± SD (mg/dL); median (P25; P75)	167.6 ± 25.1; 175 (154; 186)
OGTT 120' mean ± SD (mg/dL); median (P25; P75)	146.4 ± 26.8; 154 (129; 164)
Week of diagnosis, mean ± SD	18.0 ± 8.8
median (P25; P75)	24 (9; 26)
Week of 1st hospital appointment, mean ± SD	23.4 ± 8.4
median (P25; P75)	26 (15; 30)
Weeks from diagnosis until 1st appointment, mean ± SD	5.3 ± 4.7
median (P25; P75)	4 (2; 7)
Gestational weight gain, mean ± SD (kg)	10.5 ± 5.4
median (P25; P75)	11.0 (7; 14.4)
Adequate, n (%)	4372 (32.5%)
Insufficient, n (%)	5245 (38.9%)
Excessive, n (%)	3850 (28.6%)
Treatment of GD, n (%)	
Diet and exercise, n (%)	7856 (59.4%)
Only insulin, n (%)	3143 (23.8%)
Only OHD, n (%)	1495 (11.3%)
Insulin and OHD, n (%)	729 (5.5%)
Daily dosage of insulin, mean ± SD (units)	20.7 ± 18.7
median (P25; P75)	15 (8; 27)
Daily dosage of metformin, mean ± SD (g)	1414.6 ± 681.7
median (P25; P75)	1400 (1000; 2000)
Week of delivery, mean ± SD; median (P25; P75)	38.5 ± 1.5; 39 (38; 39)
Eutocic delivery, n (%)	6585 (48.9%)
Dystocic delivery, n (%)	6560 (48.7%)
Caesarean section, n (%)	4348 (66.3%)
Urgent, n (%)	2170 (49.9%)
Elective, n (%)	1805 (41.5%)
Birthweight of newborn, mean ± SD (g)	3180.7 ± 489.4
median (P25; P75)	3200 (2900; 3480)

BMI: body mass index; GD: gestational diabetes; n: number; OGTT: oral glucose tolerance test; OHD: oral hypoglycaemic drug; P25: percentile 25; P75: percentile 75; SD: standard deviation; 0': zero minutes; 60': 60 minutes; 120': 120 minutes

Table 2 – Association between maternal and neonatal complications and pregestational BMI (according to WHO)

Variables	BMI categories				*p* value
	Underweight (< 18.5 kg/m²) (n = 261)	**Normal** (18.5 - 24.9 kg/m²) (n = 5550)	**Overweight** (25 - 29.9 kg/m²) (n = 4064)	**Obesity** (≥ 30 kg/m²) (n = 3592)	
Maternal morbidity, n (%)*	26 (10.0%)	601 (10.8%)	602 (14.8%)	813 (22.6%)	**< 0.001**
Abortion, n (%)	0 (0%)	16 (0.3%)	12 (0.3%)	8 (0.2%)	0.757
Gestational hypertension, n (%)	3 (1.1%)	136 (2.5%)	166 (4.1%)	243 (6.8%)	**< 0.001**
Preeclampsia, n (%)	2 (0.8%)	90 (1.6%)	112 (2.8%)	161 (4.5%)	**< 0.001**
Hydramnios, n (%)	6 (2.3%)	102 (1.8%)	95 (2.3%)	91 (2.5%)	0.131
Fetal death, n (%)	1 (0.4%)	9 (0.2%)	12 (0.3%)	10 (0.3%)	0.496
Caesarean section, n (%)	60 (23.0%)	1552 (28.0%)	1323 (32.6%)	1413 (39.3%)	**< 0.001**
Neonatal death, n (%)	0 (0%)	8 (0.1%)	8 (0.2%)	5 (0.1%)	0.763
Neonatal morbidity, n (%)	42 (16.1%)	973 (17.5%)	740 (18.2%)	739 (20.6%)	**0.015**
Neonatal hypoglycaemia, n (%)	9 (3.4%)	215 (3.9%)	178 (4.4%)	157 (4.4%)	0.768
Hyperbilirubinemia, n (%)	25 (9.6%)	572 (10.3%)	450 (11.1%)	450 (12.5%)	**0.034**
Respiratory distress syndrome, n (%)	4 (1.5%)	155 (2.8%)	123 (3.0%)	131 (3.6%)	0.151
NICU hospitalization, n (%)	20 (7.7%)	362 (6.5%)	273 (6.7%)	275 (7.7%)	0.387
Prematurity (< 37 weeks), n (%)	33 (12.6%)	357 (6.4%)	284 (7.0%)	223 (6.2%)	**0.001**
Macrosomia (≥ 4000 g), n (%)	1 (0.4%)	124 (2.2%)	153 (3.8%)	233 (6.5%)	**< 0.001**
Low birthweight (< 2500 g), n (%)	36 (13.8%)	442 (8.0%)	288 (7.1%)	199 (5.5%)	**< 0.001**
Large for gestational age (Fenton charts), n (%)	1 (0.4%)	130 (2.3%)	156 (3.8%)	248 (6.9%)	**< 0.001**
Large for gestational age (Portuguese charts), n (%)	7 (2.7%)	384 (6.9%)	433 (10.7%)	627 (17.5%)	**< 0.001**
Small for gestational age (Fenton charts), n (%)	50 (19.2%)	807 (14.5%)	428 (10.5%)	306 (8.5%)	**< 0.001**
Small for gestational age (Portuguese charts), n (%)	51 (19.5%)	696 (12.5%)	362 (8.9%)	258 (7.2%)	**< 0.001**
Trauma during delivery, n (%)	1 (0.4%)	68 (1.4%)	64 (1.7%)	74 (2.3%)	**0.007**
Congenital abnormalities, n (%)	8 (3.1%)	216 (3.9%)	156 (3.8%)	117 (3.3%)	0.248
Postpartum reclassification†					
Normal, n (%)	155 (59.4%)	3663 (66.0%)	2650 (65.2%)	2232 (62.1%)	**< 0.001**
Impaired fasting glucose, n (%)	1 (0.4%)	23 (0.4%)	30 (0.7%)	37 (1.0%)	**< 0.001**
Impaired glucose tolerance, n (%)	11 (4.2%)	179 (3.2%)	148 (3.6%)	158 (4.4%)	**< 0.001**
Diabetes mellitus, n (%)	3 (1.1%)	14 (0.3%)	26 (0.6%)	17 (0.5%)	**< 0.001**

BMI: body mass index; NICU: neonatal intensive care unit; n: number; WHO: World Health Organization

*: besides the ones listed below, includes other complications such infections, deep vein thrombosis, hematologic disorders, coagulation disorders, hepatic cholestasis, endocrine disorders, flares of autoimmune diseases or *de novo*, asthma exacerbations, renal lithiasis, and others.

†: the missing data of postpartum reclassification are not represented in the Table

(aOR: 2.18; CI 95%: 1.47 - 3.25) or being LGA, and equally regardless of the use of the Fenton or Portuguese chart criteria (aOR: 2.03; CI 95%: 1.35 - 3.07 and aOR: 1.87; CI 95%: 1.44 - 2.41, respectively). In this sequence, previous overweight or obese was associated with a decreased risk of SGA in both Fenton and Portuguese charts (aOR: 0.73; CI 95%: 0.57 - 0.94; aOR: 0.64; CI 95%: 0.49 - 0.84 and aOR: 0.69; CI 95%: 0.52 - 0.92; aOR: 0.66; CI 95%: 0.49 - 0.90) and obesity alone was associated with decreased risk for low birthweight (aOR: 0.62; CI 95%: 0.47 - 0.83) (Table 4).

Regarding GWG, all neonatal complications showed statistically significant differences between the groups (Table 3).

When facing an excessive GWG, the risk of macrosomia (aOR: 2.02; CI 95%: 1.40 - 2.91) and LGA by Fenton and Portuguese charts (aOR: 1.94; CI 95%: 1.35 - 2.78 and aOR: 1.92; CI 95%: 1.51 - 2.45, respectively) were increased. Despite that, insufficient GWG was associated with an increased risk of low birthweight (aOR: 1.36; CI 95%: 1.06 - 1.74) and SGA according to the Fenton charts (aOR: 1.40; CI 95%: 1.09 - 1.79) and decreased risk of LGA according to Portuguese charts (aOR: 0.74; CI 95%: 0.57 - 0.96) (Table 5).

Moreover, different categories of BMI and GWG groups affected the postpartum reclassification (Tables 2 and 3). Previously underweight, overweight, and obese patients were more associated with glycemic abnormalities during reclassification. Excessive GWG was associated with impaired fasting glucose, whilst insufficient GWG was associated with impaired glucose tolerance and diabetes mellitus. Nonetheless, after examining the association by logistic

Table 3 – Association between maternal and neonatal complications and GWG (according to IOM)

Variables	GWG			*p* value
	Adequate (n = 4372)	Insufficient (n = 5245)	Excessive (n = 3850)	
Maternal morbidity, n (%)*	639 (14.6%)	724 (13.8%)	679 (17.6%)	**< 0.001**
Abortion, n (%)	7 (0.2%)	26 (0.5%)	3 (0.1%)	**< 0.001**
Gestational hypertension, n (%)	164 (3.8%)	157 (3.0%)	227 (5.9%)	**< 0.001**
Preeclampsia, n (%)	123 (2.8%)	99 (1.9%)	143 (3.7%)	**< 0.001**
Hydramnios, n (%)	87 (2.0%)	90 (1.7%)	117 (3.0%)	**< 0.001**
Fetal death, n (%)	11 (0.3%)	14 (0.3%)	7 (0.2%)	0.694
Caesarean section, n (%)	1415 (32.4%)	1516 (28.9%)	1417 (36.8%)	**< 0.001**
Neonatal death, n (%)	5 (0.1%)	9 (0.2%)	7 (0.2%)	**0.003**
Neonatal morbidity, n (%)	834 (19.1%)	909 (17.3%)	751 (19.5%)	**< 0.001**
Neonatal hypoglycaemia, n (%)	173 (4.0%)	221 (4.2%)	165 (4.3%)	**0.044**
Hyperbilirubinemia, n (%)	501 (11.5%)	536 (10.2%)	460 (11.9%)	**0.001**
Respiratory distress syndrome, n (%)	119 (2.7%)	162 (3.1%)	132 (3.4%)	**0.007**
NICU hospitalization, n (%)	284 (6.5%)	367 (7.0%)	279 (7.2%)	**0.022**
Prematurity (< 37 weeks), n (%)	292 (6.7%)	402 (7.7%)	203 (5.3%)	**< 0.001**
Macrosomia (≥ 4000 g), n (%)	130 (3.0%)	104 (2.0%)	277 (7.2%)	**< 0.001**
Low birthweight (< 2500 g), n (%)	286 (6.5%)	492 (9.4%)	187 (4.9%)	**< 0.001**
Large for gestational age (Fenton charts), n (%)	146 (3.3%)	114 (2.2%)	275 (7.1%)	**< 0.001**
Large for gestational age (Portuguese charts), n (%)	428 (9.8%)	341 (6.5%)	682 (17.7%)	**< 0.001**
Small for gestational age (Fenton charts), n (%)	479 (11.0%)	784 (14.9%)	328 (8.5%)	**< 0.001**
Small for gestational age (Portuguese charts), n (%)	416 (9.5%)	674 (12.9%)	277 (7.2%)	**< 0.001**
Trauma during delivery, n (%)	60 (1.5%)	60 (1.3%)	87 (2.5%)	**< 0.001**
Congenital abnormalities, n (%)	176 (4.0%)	173 (3.3%)	148 (3.8%)	**< 0.001**
Postpartum reclassification†				
Normal, n (%)	2858 (65.4%)	3518 (67.1%)	2324 (60.4%)	**< 0.001**
Impaired fasting glucose, n (%)	31 (0.7%)	29 (0.6%)	31 (0.8%)	**< 0.001**
Impaired glucose tolerance, n (%)	155 (3.5%)	212 (4.0%)	129 (3.4%)	**< 0.001**
Diabetes mellitus, n (%)	18 (0.4%)	26 (0.5%)	16 (0.4%)	**< 0.001**

GWG: gestational weight gain; IOM: Institute of Medicine; NICU: neonatal intensive care unit; n: number
*: besides the ones listed below, includes other complications such infections, deep vein thrombosis, hematologic disorders, coagulation disorders, hepatic cholestasis, endocrine disorders, flares of autoimmune diseases or *de novo*, asthma exacerbations, renal lithiasis, and others.
†: the missing data of postpartum reclassification are not represented in the Table

regression analysis, only crude [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)], and not adjusted, associations showed that being overweight was associated with an increased risk of impaired fasting glucose (OR: 1.80; CI 95%: 1.05 - 3.11) and diabetes mellitus (OR: 2.57; CI 95%: 1.34 - 4.93) at postpartum reclassification. As for pregestational obesity, it was associated with an increased odds of impaired fasting glucose (OR: 2.64; CI 95%: 1.57 - 4.45) and impaired glucose tolerance (OR: 1.45; CI 95%: 1.16 - 1.81) at reclassification. The underweight category had a very high odds of being reclassified as diabetic at postpartum (OR: 5.06; CI 95%: 1.44 - 17.80) [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

Regarding the different GWG categories, no association with statistical significance was demonstrated via multinomial logistic regression [Appendix 1, Table 4 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15896/Appendix_01.pdf)].

DISCUSSION

Our study showed that BMI above 25 kg/m^2 was associated with an increased risk of maternal morbidity, such as gestational hypertension and Caesarean delivery whilst being associated with a decreased risk of small for gestational age newborns, which corroborates the findings made by Gonçalves *et al*.[8] BMI equal or higher than 30 kg/m^2 was associated with an increased risk of preeclampsia, a very serious condition threatening the life of both mother and child. Additionally, pregestational obesity was associated with a higher number of RDS events, NICU hospitalization, macrosomia and LGA newborns, even though with a smaller

Table 4 – Adjusted association* by logistic regression between pregnancy and neonatal complications and pregestational BMI (according to WHO)

Dichotomous and multinomial outcomes†	BMI categories						
	Underweight (< 18.5 kg/m²) aOR (CI 95%)	***p* value**	**Normal** (18.5 - 24.9 kg/m²) aOR (CI 95%)	**Overweight** (25 - 29.9 kg/m²) aOR (CI 95%)	***p* value**	**Obesity** (≥ 30 kg/m²) aOR (CI 95%)	***p* value**
Maternal morbidity	0.87 (0.43 - 1.76)	0.699	1.00	**1.31 (1.06 - 1.61)**	**0.012**	**2.42 (1.99 - 2.94)**	**< 0.001**
Gestational hypertension	0.92 (0.22 - 3.90)	0.910	1.00	**1.56 (1.05 - 2.31)**	**0.029**	**2.79 (1.94 - 4.02)**	**< 0.001**
Preeclampsia	0.62 (0.08 - 4.91)	0.652	1.00	1.54 (0.94 - 2.54)	0.088	**3.05 (1.93 - 4.82)**	**< 0.001**
Hydramnios	2.03 (0.42 - 9.81)	0.380	1.00	0.87 (0.48 - 1.57)	0.642	1.10 (0.63 - 1.91)	0.744
Caesarean section	1.22 (0.67 - 2.23)	0.514	1.00	**1.22 (1.02 - 1.46)**	**0.032**	**1.77 (1.48 - 2.11)**	**< 0.001**
Neonatal morbidity	0.74 (0.42 - 1.30)	0.293	1.00	0.97 (0.82 - 1.15)	0.762	1.16 (0.98 - 1.37)	0.093
Neonatal hyperbilirubinemia	0.74 (0.37 - 1.50)	0.405	1.00	1.01 (0.82 - 1.24)	0.923	1.13 (0.92 - 1.39)	0.243
Respiratory distress syndrome	0.36 (0.04 - 2.99)	0.347	1.00	1.10 (0.71 - 1.70)	0.665	**1.69 (1.14 - 2.51)**	**0.010**
NICU hospitalization	1.15 (0.51 - 2.60)	0.731	1.00	1.14 (0.87 - 1.49)	0.347	**1.54 (1.19 - 1.99)**	**0.001**
Prematurity (< 37 weeks)	0.92 (0.28 - 3.00)	0.885	1.00	1.25 (0.90 -1.74)	0.178	1.31 (0.95 - 1.81)	0.101
Macrosomia (≥ 4000 g)	0.00 (0.00)	0.997	1.00	1.19 (0.77 - 1.84)	0.442	**2.18 (1.47 - 3.25)**	**< 0.001**
Low birthweight (< 2500 g)	1.48 (0.75 - 2.91)	0.262	1.00	0.92 (0.71 - 1.18)	0.500	**0.62 (0.47 - 0.83)**	**0.001**
Large for gestational age (Fenton charts)	0.00 (0.00)	0.996	1.00	1.26 (0.81 - 1.97)	0.305	**2.03 (1.35 - 3.07)**	**0.001**
Large for gestational age (Portuguese charts)	0.19 (0.03 - 1.47)	0.112	1.00	1.05 (0.80 - 1.38)	0.731	**1.87 (1.44 - 2.41)**	**< 0.001**
Small for gestational age (Fenton charts)	1.31 (0.67 - 2.58)	0.436	1.00	**0.73 (0.57 - 0.94)**	**0.016**	**0.64 (0.49 - 0.84)**	**0.001**
Small for gestational age (Portuguese charts)	1.54 (0.75 - 3.15)	0.238	1.00	**0.69 (0.52 - 0.92)**	**0.012**	**0.66 (0.49 - 0.90)**	**0.007**
Trauma during delivery	0.00 (0.00)	0.997	1.00	1.22 (0.72 - 2.06)	0.458	1.23 (0.73 - 2.08)	0.435
Postpartum reclassification†							
Normal	1.00		1.00	1.00		1.00	
Impaired fasting glucose	1.39 (0.18 - 10.94)	0.756	1.00	1.03 (0.52 - 2.07)	0.928	0.97 (0.49 - 1.92)	0.927
Impaired glucose tolerance	0.00 (0.00)		1.00	1.16 (0.78 - 1.73)	0.473	1.43 (0.98 - 2.10)	0.065
Diabetes mellitus	3.66 (0.67 - 20.05)	0.134	1.00	1.35 (0.60 - 3.06)	0.469	0.58 (0.23 - 1.43)	0.233

aOR: adjusted odds ratio; BMI: body mass index; CI 95%: confidence intervals at 95%; NICU: neonatal intensive care unit; WHO: World Health Organization

*: adjusted for maternal age, number of previous abortions/deliveries, first-degree family history of diabetes, previous macrosomia, fasting glucose, weeks between diagnosis and 1st hospital appointment, GD treatment, GWG group and week of delivery.

†: postpartum reclassification was analyzed as a multinomial outcome. All other classifications were compared with the standard, the "normal" classification.

number of low birthweight newborns.

With regards to GWG groups according to IOM, the analysis demonstrated that insufficient weight gain was associated with lower risk of gestational hypertension, preeclampsia, caesarean section and LGA babies (only those defined by the Portuguese charts). However, insufficient weight gain was associated with a higher odd of low birthweight and SGA according to the Fenton charts, which concurs with the study of Gonçalves *et al*.[8] These results reflect the prospective study of Lima *et al* based on a population of pregnant women in Sweden, demonstrating that previously obese participants with insufficient GWG would be associated with a reduced risk of preeclampsia, caesarean deliveries and LGA newborns, although they would be associated, on the other hand, with an increased risk of SGA newborns.[14]

Regarding excessive GWG, it was associated with higher risk of gestational hypertension, hydramnios, macrosomia, and LGA (according to both the Fenton and the Portuguese charts) newborns, as seen in many other studies.[16-20]

About postpartum reclassification, only the crude associations demonstrated statistically significant differences that were lost after adjustment for other variables. This means that the presence of such association was possible due to the presence of other risk factors, such as maternal age, family history of diabetes and treatment used for GD. By comparison between crude and adjusted ORs, we may say that there was a confounding effect in our study, and therefore adjusted OR should be prioritized.

It is important to mention the limitations of our work. Because of its retrospective nature, based on data previously present in the national registry of GD, we observed missing data and lack of consistency as well as high variability in the data collected, leading to an information bias due to the variability of the observer and the interviewer.

The information contained in the registry is not representative of the whole country, because the participation of each hospital/maternity hospital in terms of data collection is not mandatory and most of the peripheral hospitals are not represented in the registry, demonstrating a selection bias by participation bias.

Most of the maternal information was self-reported, leading to an information bias caused by measurement, memory, and social desirability bias.

In order to reduce the limitations of the study and the amount of biases, it is necessary to develop prospective studies with previous standardized data collection procedures and training of the personnel involved in this process.

CONCLUSION

Both pregestational BMI and GWG have a significant impact on maternal and neonatal outcomes during pregnancy and the postnatal period in women diagnosed with gestational diabetes. Our findings suggested positive associations between BMI and GWG and gestational hypertension, preeclampsia, hydramnios, caesarean delivery, RDS, NICU admission, birthweight, and LGA/SGA.

When comparing pregestational BMI and GWG, the first was more significantly associated with obstetric and neonatal complications, similar to the meta-analysis of LifeCycle Project-Maternal Obesity and Childhood Outcomes Study Group.[27] Nonetheless, they are independent risk factor predictors that need monitoring and control to minimize the complications in GD pregnant women.

Table 5 – Adjusted association* by logistic regression between maternal and neonatal complications and GWG (according to IOM)

Dichotomous outcomes	GWG				
	Adequate aOR (CI 95%)	Insufficient aOR (CI 95%)	*p* value	Excessive aOR (CI 95%)	*p* value
Maternal morbidity	1.00	0.86 (0.71 - 1.04)	0.119	1.14 (0.94 - 1.39)	0.189
Abortion	1.00	0.00 (0.00)	0.982	2.05 (0.17 - 24.62)	0.570
Gestational hypertension	1.00	**0.69 (0.48 - 0.98)**	**0.039**	**1.53 (1.11 - 2.12)**	**0.010**
Preeclampsia	1.00	**0.44 (0.28 - 0.68)**	**< 0.001**	1.26 (0.86 - 1.85)	0.237
Hydramnios	1.00	0.98 (0.55 - 1.72)	0.933	**2.05 (1.19 - 3.53)**	**0.010**
Caesarean section	1.00	**0.81 (0.69 - 0.96)**	**0.015**	1.15 (0.96 - 1.37)	0.138
Neonatal complications					
Prematurity (< 37 weeks)	1.00	1.07 (0.79 - 1.44)	0.673	0.93 (0.66 - 1.31)	0.671
Macrosomia (≥ 4000 g)	1.00	0.72 (0.47 - 1.09)	0.120	**2.02 (1.40 - 2.91)**	**< 0.001**
Low birthweight (< 2500 g)	1.00	**1.36 (1.06 - 1.74)**	**0.016**	0.85 (0.63 - 1.14)	0.278
Large for gestational age (Fenton charts)	1.00	0.74 (0.49 - 1.11)	0.143	**1.94 (1.35 - 2.78)**	**< 0.001**
Large for gestational age (Portuguese charts)	1.00	**0.74 (0.57 - 0.96)**	**0.021**	**1.92 (1.51 - 2.45)**	**< 0.001**
Small for gestational age (Fenton charts)	1.00	**1.40 (1.09 - 1.79)**	**0.007**	0.97 (0.72 - 1.31)	0.864
Small for gestational age (Portuguese charts)	1.00	1.19 (0.90 - 1.56)	0.219	0.97 (0.70 - 1.36)	0.869
Trauma during delivery	1.00	0.61 (0.36 - 1.06)	0.077	1.40 (0.87 - 2.26)	0.170

aOR: adjusted odds ratio; CI 95%: confidence intervals at 95%; GWG: gestational weight gain; IOM: Institute of Medicine; NICU: neonatal intensive care unit

*: adjusted for maternal age, number of previous abortions/deliveries, first degree family history of diabetes, previous macrosomia, fasting glucose, weeks between diagnosis and first hospital appointment, GD treatment, BMI category and week of delivery.

In conclusion, an adequate surveillance before conception and a strict follow-up during pregnancy are essential, to reduce risks and to decrease the predisposition of these newborns to severe outcomes.

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AUTHORS' CONTRIBUTION

JCX: contributed to conception and design, acquisition of data, analysis, and interpretation of data, drafting and revising the article and giving the final approval of the version to be published. This author, as guarantor, accepts full responsibility for the work.

ÂC: contributed to conception and design, acquisition of data, revising the article and providing the final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors declare not having any competing interests related to this paper.

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Interpersonal Relationships in Diabetes: Views and Experience of People with Diabetes, Informal Carers, and Healthcare Professionals in Portugal

ARTIGO ORIGINAL

Relações Interpessoais na Diabetes: Perspetiva e Experiência de Pessoas com Diabetes, Cuidadores Informais, e Profissionais de Saúde em Portugal

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ABSTRACT

Introduction: The increasing burden of diabetes poses a great challenge to healthcare systems and economy worldwide. Although modern therapeutic strategies for diabetes are widely available, most patients still fail to achieve optimal clinical targets and well-being. The primary objective of this study was to assess and explore potential drivers and successful management of diabetes among people with diabetes, family members and healthcare professionals in Portugal, by applying the protocol of the multinational study "Diabetes, Attitudes, Wishes and Needs (DAWN2)".

Material and Methods: A total of 767 adults, including 417 people with diabetes, 123 family members and 227 healthcare professionals, participated in the study. Surveys assessed health-related quality of life, self-management, attitudes/beliefs, social support and priorities for improvement areas in diabetes care.

Results: Diabetes has a negative impact on the physical health and emotional well-being of patients in Portugal and is also a psychological burden for family members. Earlier diagnosis and treatment of diabetes were mentioned as a major area of improvement. Healthcare professionals indicated the need for diabetes self-management education.

Conclusion: We have used for the first time in Portugal the DAWN2 protocol to address the wishes, needs, and attitudes of Portuguese diabetes patients, their relatives, and healthcare professionals regarding the disease.

Keywords: Diabetes Mellitus; Portugal; Quality of Life; Self-Management; Social Support

RESUMO

Introdução: Os encargos crescentes com a diabetes representam um desafio para os sistemas de saúde e economia a nível mundial. Apesar de terapias modernas para a diabetes disponíveis, a maioria das pessoas continua privada de cuidados e bem-estar adequados. O objetivo primário deste estudo foi avaliar e explorar os fatores relevantes para o controlo ativo e eficaz da diabetes para as pessoas com diabetes, familiares e profissionais de saúde em Portugal, aplicando o protocolo do estudo multinacional "*Diabetes, Attitudes, Wishes and Needs* (DAWN2)".

Material e Métodos: Participaram no estudo 767 adultos (417 pessoas com diabetes, 123 familiares e 227 profissionais de saúde). Foram avaliados a qualidade de vida associada à saúde, autogestão, atitudes/crenças, apoio social e prioridades em áreas de melhoria no tratamento da diabetes.

Resultados: A diabetes tem um impacto negativo na saúde física e no bem-estar emocional das pessoas em Portugal, sendo também uma carga psicológica para os seus familiares. O diagnóstico e tratamento precoces da diabetes foram indicados como a principal área de melhoria. Profissionais de saúde indicaram a necessidade de educação para a autogestão da diabetes.

Conclusão: Pela primeira vez em Portugal usámos o protocolo DAWN2 para ir ao encontro dos desejos, necessidades e atitudes dos doentes Portugueses com diabetes, os seus familiares e profissionais de saúde relativamente à doença.

Palavras-chave: Apoio Social; Autogestão; Diabetes Mellitus; Portugal; Qualidade de Vida

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic disease that requires continuous medical care.[1] Over the past few decades, ageing and unhealthy lifestyles have been contributing to the increased prevalence of type 2 diabetes (T2D), posing an growing challenge to healthcare systems and national economies.[2,3] In order to prevent or delay DM short- and long-term complications, it is necessary to implement an extensive self-management program of the disease, which should include the adoption of healthy food habits, physical activity, monitoring of blood glucose levels and, if necessary, compliance with medical therapy.[2,4,5]

People with diabetes (PWD) often describe their experiences of managing the disease as emotionally, physically and socially challenging.[6] Family members may have an active and very important role in supporting and caring for people with diabetes, contributing to patient compliance with treatment and promoting the change and maintenance of a healthy life style in terms of diet and physical

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activity.[7,8] Health care providers (HCPs) are also an important element of the patient support network, by playing a significant role in encouraging patients to improve their quality of life.[9] Nevertheless, despite all psychosocial and educational support programs for PWD implemented over the last decade, many patients still do not have access to adequate care and support.[10]

The Diabetes Attitudes, Wishes and Needs 2 (DAWN2), is a multinational, interdisciplinary and multi-stakeholder study, aiming to assess and explore potential drivers for active and successful diabetes management among people with diabetes, family members, and healthcare professionals, in response to growing pressure for more cost-effective models of diabetes care.[10] The DAWN2 protocol is based on three quantitative surveys which explore the experiences and unmet needs of PWD, family members of PWD and healthcare professionals treating PWD. The aim of the study was to generate insights that can promote the development of innovative efforts by all stakeholders to improve the self-management and psychosocial support of people with diabetes. Data from 17 countries using the DAWN2 protocol has been published and areas for improvement as well as best practices were identified that can be used to drive the changes that improve the PWD outcomes.[11]

Here, we report the application of the DAWN2 protocol to the Portuguese setting. We aim to identify unmet needs and benchmark our insights with data from other countries, so that we can contribute to the specific for the Portuguese context for improvement of PWD management and support.

MATERIAL AND METHODS

Participants

The composition of the study population was conceived to portray in a representative manner the population of adults diagnosed with diabetes and their families in Portugal, according to the DAWN2 protocol.[10] All relevant healthcare professionals – endocrinologists, internal medicine specialists, primary care physician (PCP) / general practitioners (GPs) / family physicians (FPs), nurses, dietitians, etc. – were included, in order to provide an integrated view of the healthcare provided to the population with diabetes in Portugal.

A total of 767 participants were included in the study: 417 PWD, 123 family members/carers (FMs) and 227 HCPs. PWD were divided into type 1 DM patients (n = 89) and type 2 DM patients (n = 238), of which 170 were non-insulin treated and 158 were insulin treated. FMs were divided into insulin treated relative (n = 86) and non-insulin treated relative (n = 37). HCPs were divided into primary care physicians / GPs / FPs (n = 68), endocrinologists / internal medicine specialists (n = 40) and NDO's – nurses, dietitians and other HCPs (n = 119).

The inclusion criteria for the PWD group were diagnosis of diabetes (type 1 or type 2) and for the FMs group was to be involved in the daily care of an adult with type 1 or type 2 diabetes. The inclusion criteria for the HCP group were as follows: PCP/GP/FP providing care for five or more adults with diabetes per month; endocrinologists or internal medicine specialists providing care for 50 or more adults with diabetes per month, and prescribing oral medication, insulin or other injectable medication for diabetes. The inclusion criteria for NDOs were to be general practice/diabetes nurses, dietitians, psychologists or other healthcare professionals, providing care for five or more adults with diabetes per month. All study participants were adults (18 years old or more), were living in Portugal and agreed to participate in the survey upon review of the provided informed consent form.

Subjects diagnosed with diabetes for less than 12 months before the recruitment were excluded, as well as participants with gestational diabetes or without verbal or writing comprehension ability.

The sample source differs between groups of participants, but a convenience sampling method was adopted, using social events and platforms from the Portuguese Diabetes Association (APDP). The duration of the interviews was 40 to 60 minutes, depending on the specific group. On-site recruitment was adopted in all cases, except for the HCP group, where some participants were recruited by e-mail.

Setting and study design

This was a cross-sectional study, aiming to achieve a reliable description of the psychosocial factors involving adults with diabetes, their families and healthcare professionals in Portugal. Data from the PWD and FMs groups was collected between January and July 2017. Data from HCPs were collected between January 2017 and April 2018. For the PWD group, 76 telephone and 341 face-to-face interviews were conducted. For the FMs survey, 53 telephone and 70 face-to-face interviews were conducted. In the HCPs group, 227 answered the surveys online, in a self-reported manner. All interviews were conducted in European Portuguese. The name of the sponsor of the study was not disclosed in any of the survey materials.

Data sources

Three separate survey questionnaires, one for each of the three target study groups (i.e. PWD, FMs, HCPs) were developed. The survey questionnaires incorporated items from the original DAWN study[12] and new questions, including open-ended items developed by a multidisciplinary, multinational team.[10] The surveys included standardized scoring scales – the abbreviated version of WHO quality of life assessment questionnaire – (WHOQOL-BREF); EuroQol (EQ-5D); WHO Well-Being index (WHO-5); the Problem Areas in Diabetes scale – short form (PAID-5); the Health Care Climate questionnaire (HCCC); the Summary of Diabetes Self-Care Activities measure (SDSCA) - and also new questions adapted from existing validated instruments - the Diabetes Empowerment scale-short form (DES-SF), Patient Assessment of Chronic Illness Care (PACIC), and Diabetes Family Behaviour checklist (DFBC).

The scoring scales were translated into Portuguese.

The translations were reviewed by a panel of Portuguese diabetes experts. Selected questions intended for scientific benchmarking were back translated into English by a third independent professional translator and an harmonization review was undertaken, involving the approval of academic experts and of the original authors of the scientific scales.

Statistical analysis

The responses from participants who completed the survey on face-to-face or telephone interviews were entered in the online survey program by interviewers, using a unique survey link for each participant. Statistical analysis was performed using the Statistical Package for the Social Sciences Software (SPSS 24.0®). Descriptive statistics were calculated for all the study variables, including frequencies, percentages, mean and standard deviation, as applicable. For the analysis of PWD data, Type 2 DM patients were analysed as a whole (n = 328), and also in two subgroups - non-insulin treated (n = 170) and insulin treated (n = 158).

Ethical considerations

The DAWN2 study was conducted in accordance with ICH-GCP, the Helsinki Declaration and national legislation and was submitted and obtained favourable opinion from the local APDP Ethics Committee before implementation. Those interested in participating were requested to provide informed written consent.

Confidentiality

All data was collected anonymously and there was no way to relate the completed surveys with the participants. The DAWN2 study was submitted and approved by the Portuguese Data Protection Authority (CNPD – Comissão Nacional de Proteção de Dados) before implementation. Approval number 12008/2016, dated 09/November/2016.

RESULTS

Demographic characterization

Table 1 summarizes the characteristics of PWD group. In both type 1 and type 2 groups, most subjects were male (51.7%, n = 46 and 55.8%, n = 183, respectively). Type 1 PWD were mostly aged from 18 to 59 years old (85,4%), whereas type 2 PWD were mostly 60 years old or more (76.8%). On average, type 1 PWD were diagnosed at a younger age than type 2 PWD (22.9 and 48.6 years old, respectively). Most type 1 PWD (70%) reported to work full-time, whereas most type 2 PWD (63%) were retired. Most type 1 and type 2 PWD (55% and 64%, respectively) reported a monthly household income between €506 and €2000 (low / low-middle class); and 25% and 15%, respectively, an income between €2001 and €5000 (middle class). The highest education level most frequently reported by type 1 PWD were bachelor's / master's degree (44%) and secondary education (27%); whereas among type 2 PWD 43% had only finished the first cycle of the basic education, 18% the secondary education, 17% a bachelor's / master's degree, and 15% the third cycle of basic education.

FMs were divided into two groups: group 1 (n = 85), whose relatives are insulin treated, and group 2 (n = 35), whose relatives are non-insulin treated. FMs from both group 1 and group 2 were mainly female (73.3%, n = 63 and 83.8%, n = 31, respectively) and the patient's spouse/partner (group 1 - 60.5%, n = 52; group 2 - 64.9%, n = 24). On average, FMs age on group 1 was 56.4 years old, and on group 2, 63.1 years old. From the FMs on group 1, 48% reported to work full-time and 38% were retired, whereas 43% of FMs on group 2 were retired and 24% worked full-time. Of note, 2% of FMs on group 1 reported not working full-time because of PWD condition. Most FMs of group 1 and group 2 (64% and 62%, respectively) reported a monthly household income between €506 and €2000 (low / low-middle class); and 18% and 8%, respectively, an income between €2001 and €5000 (middle class). The highest education level most frequently reported by FMs on group 1 were secondary education (27%), bachelor's / master's degree (21%), first cycle of basic education (21%), and the third cycle of basic education (17%). The highest education level most frequently reported by FMs on group 2 were first cycle of basic education (38%), bachelor's / master's degree (25%), and secondary education (16%).

HCPs were divided into three groups: PCPs/GPs/FPs (n = 68); hospital based specialists (n = 40); and nurses/dietitians/other HCPs (NDOs; n = 119).hospital based specialists were either internal medicine physicians (45.0%, n = 18) or endocrinologists (55.0%, n = 22). All three HCPs groups followed mostly type 2 DM patients: PCPs/GPs – 95.6%; hospital-based specialists – 80%; and NDOs – 89%.

Living with diabetes: the perspective of the person with diabetes

Table 2 summarizes the data regarding the perceived quality of life (QoL) of PWD. Most type 1 DM patients perceived their QoL as 'Good/Very Good' (67.4%), whereas type 2 patients perceived their QoL mostly as 'Neither poor nor good' (48.5%). The perceived QoL of type 2 patients non-insulin treated reported as 'good/very good' was better than the one reported by type 2 insulin treated patients: 48.2% *vs* 39.2%. This observation was confirmed by the PAID-5 assessment scale: 50.9% of type 2 non-insulin treated patients reported 'high distress' *versus* 72.9% of type 2 insulin-treated patients.

Table 3 summarizes the impact of diabetes on PWD's QoL in six dimensions: physical health, financial situation, personal relationships, leisure activities, work or study, and emotional well-being. Physical health and emotional well-being were the most negatively impacted areas in PWD's QoL for both type 1 and type 2 patients.

PWD attitudes about diabetes were also analysed. For the sentence "I am very worried about the risk of hypoglycaemic events", type 1patients reported an agreement rating of 61.8% (n = 55) and type 2, 48.4% (n = 158). Particularly, hypoglycaemic events at night registered an agreement rating of 68.5% (n = 61) for type 1 and 37.0% (n = 11) for type 2. Regarding the sentence "I feel very anxious

Table 1 – PWD sample characterization (n = 745)

		Type 1 (n = 89)	Type 2 (n = 328)	Type 2 non-insulin treated (n = 170)	Type 2 insulin treated (n = 158)
Gender	Male	46 (51.7%)	183 (55.8%)	106 (62.4%)	77 (48.7%)
	Female	43 (48.3%)	145 (44.2%)	64 (37.6%)	81 (51.3%)
Age	18 - 39	34 (38.2%)	2 (0.6%)	0 (0.0%)	2 (1.3%)
	40 - 59	42 (47.2%)	74 (22.6%)	40 (23.5%)	34 (21.5%)
	> 60	13 (14.6%)	252 (76.8%)	130 (76.5%)	122 (77.2%)
Age at diabetes diagnostic	Mean	22.9	48.6	52.0	44.9
	SD	12.0	10.5	10.0	9.7
Insulin prescription	At diagnostics	69 (77.5%)	13 (4.0%)	2 (1.2%)	11 (7.0%)
	Within 3 months	1 (1.1%)	1 (0.3%)	0 (0.0%)	1 (0.6%)
	No	19 (21.4%)	314 (95.7%)	168 (98.8%)	146 (92.4%)
BMI	Mean	25.0	29.0	28.4	29.5
	SD	3.6	4.7	4.3	4.9
Employment					
work full-time		70%	23%	24%	21%
work part-time		8%	3%	4%	3%
not working; looking		5%	2%	1%	3%
not working; not looking		0%	6%	8%	4%
unable to work		1%	3%	1%	4%
retired		13%	63%	61%	65%
student		3%	0%	0%	0%
stay at home spouse/partner		0%	0%	1%	0%
Monthly household income					
€0 - €505		6%	13%	11%	14%
€506 - €2000		55%	64%	61%	68%
€2001 - €5000		25%	15%	17%	14%
€5001 - €10 000		2%	2%	2%	1%
€10 001 - €20 000		1%	0%	0%	0%
declined to answer		11%	6%	9%	3%
Education					
basic education – 1st cycle		8%	43%	37%	49%
basic education – 2nd cycle		7%	7%	7%	7%
basic education – 3rd cycle		14%	15%	14%	15%
secondary education		27%	18%	21%	15%
bachelor's degree		9%	4%	4%	3%
master's degree		35%	13%	16%	9%
doctoral degree		1%	0%	1%	0%
no qualifications/education		0%	0%	0%	1%
other		0%	0%	1%	0%

BMI: body mass index (calculated as weight / square height)

about my weight", the agreement rating was 38.2% (n = 34) for type 1 and 51.1% (n = 167) for type 2 patients. Both patient groups mostly agreed with the sentence "My family argues with me about how I choose to take care of my diabetes", with an agreement rating of 65.1% (n = 58) for type 1 and 66.7% (n = 218) for type 2. Regarding discrimination, 22.5% (n = 20) of type 1 and 4.9% of type 2 patients agreed with the sentence "I have been discriminated against because I have diabetes".

Caring of diabetes: the role of family members

The quality of life of FM was also evaluated using the WHOQOL-BREF scale and WHO-5. Most FMs of type 1 patients, 59.3% (n = 19), classified their QoL as 'Good/Very

Table 2 – PWD perceived quality of life

		Type 1 (n = 89)	Type 2 (n = 328)	Type 2 non-insulin treated (n = 170)	Type 2 insulin treated (n = 158)
WHOQOL-BREF	Very Poor/Poor	3 (3.4%)	25 (7.6%)	8 (4.7%)	17 (10.8%)
	Neither poor nor good	26 (29.2%)	159 (48.5%)	80 (47.1%)	79 (50.0%)
	Good/Very Good	60 (67.4%)	144 (43.9%)	82 (48.2%)	62 (39.2%)
PAID-5	Low distress	25 (28.1%)	127 (38.8%)	83 (49.1%)	44 (27.8%)
	High distress	64 (71.9%)	200 (61.2%)	86 (50.9%)	114 (72.2%)

WHOQOL-BREF: abbreviated version of the World Health Organization quality of life assessment questionnaire WHQOL-100; PAID-5: Problem Areas in Diabetes scale – short form.

Table 3 – Impact of diabetes in PWD's QoL (n = 120)

		Slightly to very negative impact	No impact	Slightly to very positive impact	Not applicable
Physical health	**Type 1** (n = 89)	56 (62.9%)	24 (27.0%)	9 (10.1%)	0 (0.0%)
	Type 2 (n = 328)	159 (48.5%)	145 (44.2%)	24 (7.3%)	0 (0.0%)
Financial situation	**Type 1** (n = 89)	34 (38.2%)	54 (60.7%)	1 (1.1%)	0 (0.0%)
	Type 2 (n = 328)	120 (36.6%)	199 (60.7%)	9 (2.7%)	0 (0.0%)
RFFP	**Type 1** (n = 89)	18 (20.2%)	62 (69.7%)	7 (7.9%)	2 (2.2%)
	Type 2 (n = 328)	38 (11.6%)	273 (83.2%)	16 (4.9%)	1 (0.3%)
Leisure activities	**Type 1** (n = 89)	29 (32.6%)	53 (59.6%)	6 (6.7%)	1 (1.1%)
	Type 2 (n = 328)	61 (18.6%)	255 (77.7%)	9 (2.7%)	3 (1.0%)
Work or studies	**Type 1** (n = 89)	24 (27.0%)	47 (52.8%)	3 (3.4%)	15 (16.8%)
	Type 2 (n = 328)	17 (5.2%)	95 (29.0%)	3 (0.9%)	213 (64.9%)
Emotional well-being	**Type 1** (n = 89)	50 (56.1%)	35 (39.3%)	4 (4.6%)	0 (0.0%)
	Type 2 (n = 328)	139 (41.9%)	185 (56.4%)	4 (1.2%)	0 (0.0%)

PWD: person with diabetes; QoL: quality of life; RFFP: relationships with family, friends and peers

Good', 39.5% (n = 12) as 'Neither poor nor good' and 1.1% (n = 1) as 'Very Poor/Poor'. The majority of FMs of type 2 patients, 45.9% (n = 42), classified their QoL as 'Neither poor nor good', 43.2% (n = 39) as 'Good/Very Good', and 10.8% (n = 10) as 'Very Poor/Poor'. Table 4 summarizes the impact of diabetes on FM's QoL in the same six dimensions analysed for PWD plus one: relationship with the PWD the FM lives with. Emotional well-being and physical health were reported as the areas that were most negatively impacted area in FM's QoL, for both types of DM patients.

FMs attitudes about PWD condition were also analysed. For the sentence "I am very worried about the risk of hypoglycaemic events", FMs of type 1 PWD reported an agreement rating of 66% and FMs of type 2 PWD, 46%. Most FMs reported an agreement for the sentence "we argue about how PWD choses to take care of diabetes": 72% for FMs of type 1 PWD and 81% for FMs of type 2 PWD. Yet, most FMs reported an agreement for the sentence "PWD diabetes is currently well controlled: 56% for FMs of type 1 PWD and 79% for FMs of type 2 PWD.

When PWD were asked about if they inform FM about the best way to support their diabetes management, both 51.6% of type 1 (n = 46) and 16.2% of type 2 patients (n = 250) reported that they never/rarely did it. Most FMs also pointed out that the PWD they lived with never/rarely did it: with 58.1% (n = 50) for type 1 and 71.4% (n = 25) for type 2 patients. Similar results were obtained for how often PWD ask for help in diabetes management: most type 1 PWD (54.0%; n = 48), and type 2 PWD (75.6%; n = 248) reported that they never/rarely do it. Most FMs also reported that they were never/rarely asked for help: 58.1% (n = 50) for type 1 and 71.5% (n = 25) for type 2 patients.

Considering diabetes care responsibility, FMs' answers showed that PWD are mainly responsible for it: remembering to take his/her medication (type 1 - 59.3%; n = 51; type 2 - 74.3%; n = 26); measuring his/her blood sugar (type 1 - 81.4%; n = 70; type 2 - 77.2%; n = 27); injecting his/her medication (type 1 - 80.2%; n = 69; type 2 – not assessed); and planning time for exercise or physical activity (type 1 - 47.7%; n = 41; type 2 - 48.6%; n = 17). Still, FMs are the main responsible in planning and cooking healthy meals (type 1 - 34.9%; n = 30; type 2 - 37.2%; n = 13).

FMs reported high agreement scores on the following sentences: "you usually attend his/her visits to the HCPs regarding his/her diabetes" (type 1 - 82.4%; n = 52; type 2 - 80.0%; n = 28); "you wish the person you live with would take greater responsibility in caring for his/her diabetes" (type 1 - 60.4%; n = 70; type 2 - 48.5%; n = 17); and "you are confident that the person you live with can manage his/her diabetes without your help" (type 1 - 62.8%; n = 54; type 2 - 54.2%; n = 19).

Regarding supportive behaviours, PWD reported that FMs often/always warn them if they are not managing diabetes properly (type 1 - 60.0%; n = 39; type 2 - 65.0%;

Table 4 – Impact of diabetes in FM's QoL (n = 120)

		Slightly to very negative impact	No impact	Slightly to very positive impact	Not applicable
Physical health	**Group 1** (n = 85)	15 (17.6%)	58 (68.2%)	7 (8.2%)	5 (5.9%)
	Group 2 (n = 35)	6 (17.1%)	26 (74.2%)	3 (8.6%)	0 (0.0%)
Financial situation	**Group 1** (n = 85)	28 (32.9%)	52 (61.1%)	1 (1.2%)	4 (4.7%)
	Group 2 (n = 35)	12 (34.2%)	225 (62.9%)	1 (2.9%)	0 (0.0%)
RFFP	**Group 1** (n = 85)	10 (11.8%)	69 (81.2%)	4 (4.7%)	2 (2.4%)
	Group 2 (n = 35)	3 (8.6%)	28 (80.0%)	3 (8.6%)	0 (0.0%)
Leisure activities	**Group 1** (n = 85)	21 (24.7%)	56 (65.9%)	5 (5.9%)	3 (3.5%)
	Group 2 (n = 35)	3 (8.6%)	29 (82.9%)	3 (8.6%)	0 (0.0%)
Work or studies	**Group 1** (n = 85)	12 (14.1%)	32 (37.6%)	2 (2.4%)	39 (45.9%)
	Group 2 (n = 35)	0 (0.0%)	11 (31.4%)	0 (0.0%)	24 (68.6%)
Emotional well-being	**Group 1** (n = 85)	35 (41.1%)	44 (51.8%)	3 (3.5%)	3 (3.5%)
	Group 2 (n = 35)	13 (37.1%)	21 (60.0%)	1 (2.9%)	0 (0.0%)
RPWD	**Group 1** (n = 85)	19 (22.4%)	56 (65.9%)	6 (7.1%)	4 (4.7%)
	Group 2 (n = 35)	8 (22.9%)	26 (74.3%)	1 (2.9%)	0 (0.0%)

FM: family member; QoL: quality of life; RFFP: relationships with family, friends and peers; RPWD: relationship with the person with diabetes you live with

n = 117) or congratulate them otherwise (type 1 - 43.1%; n = 28; type 2 - 33.9%; n = 61). Likewise, FMs also reported the same supportive behaviour, often/always warning PWD if they believe he/she is not managing diabetes properly (type 1 - 50.6%; n = 43; type 2 - 57.1%; n = 20) or congratulating PWD otherwise (type 1 - 40.0%; n = 34; type 2 - 37.1%; n = 13). Most of PWD also reported that FMs often/always acknowledge their difficulties in living with diabetes (type 1 - 76.9%; n = 50; type 2 - 69.4%; n = 125); in line with FMs' reported perception that they take into consideration the difficulties shared by the PWD they live with (type 1 - 66.7%; n = 56; type 2 - 65.8%; n = 23).

Caring of diabetes: the perspective of health care professionals

Table 5 summarizes the data concerning the HCPs beliefs about diabetes management in three dimensions: (i) HCP understanding and management of patient emotions, (ii) HCP influence over patient management of the disease and (iii) HCP role in patient advocacy. Overall, the three groups of HCPs recognized the importance of the 3 dimensions analysed.

Regarding PACIC results for HCPs, 35.0% (n = 14) hospital-based specialists, 20.6% (n = 14) PCPs/GPs / FPs, and 27.7% (n = 34) NODs stated that they ask their patients most of the time or always how diabetes affects their life. Concerning the question "Do you ask your patients for ideas when making a diabetes care plan", the agreement scores (most of the times/always) were: 55.0% (n = 22) for hospital-based specialists; 50.0% (n = 354) for PCPs/GPs / FPs; and 43.9% (n = 54) for NODs. For the question, "Do you encourage your patients to ask questions", the agreement scores (most of the times/always) were: 77.5% (n = 31) for hospital based specialists; 75.0% (n = 51) for PCPs/GPs /FPs; and 65.8% (n = 81) for NODs.

Regarding PACIC results for PWD, 20.4% (n = 17) type 1 and 11.8% (n = 36) Type 2 patients reported that they were asked most of the time or always about how diabetes affects their life in the past 12 months. For the statement "I was helped to make plans to achieve my diabetes care goals", agreement scores (most of the time/always) were 63.8% (n = 53) for type 1 and 38.8% (n = 120) for type 2 patients. For the statement "I was helped to make plans for how to get support from friends, family or community", agreement scores (most of the time/always) were 20.4% (n = 17) for type 1 and 11.4% (n = 35) for type 2 patients. For the statement "I am satisfied that my care is well organized", agreement scores (most of the time/always) were 57.3% (n = 47) for type 1 and 48.7% (n = 149) for type 2 patients.

Table 5 – HCPs' beliefs about diabetes management, rating of "5" or "6" on a 6-point agreement scale (n = 227)

	PCPs / GPs / FPs (n = 68)	Hospital specialists* (n = 40)	NDOs (n = 119)
My success in caring for people with diabetes depends largely on my ability to understand and manage their emotional issues.	23 (33.8%)	25 (62.5%)	48 (40.3%)
HCPs have a very limited influence on how well people take care of their diabetes.	5 (7.4%)	3 (7.5%)	13 (10.9%)
It is important for me to advocate on behalf of PWD and be involved in health policy issues for improvement diabetes care.	32 (47.1%)	23 (57.5%)	46 (38.7%)

*: Endocrinologists and internal medicine specialists

HCP: healthcare professional; PCP, primary care physician; GP: general practitioner; FP: family physician; NDO: nurses, dietitian and other healthcare professionals.

Table 6 – PWD, FMs and HCPs' beliefs about areas for improvement

		Acceptance of people with diabetes as equal members of society	Convenient and safe places to participate in physical activity	Places to buy healthy and affordable food	Workplaces which it easy for people to manage their diabetes	Earlier diagnosis and treatment of diabetes
PWD	**Type 1** (n = 89)	49 (55.0%)	56 (62.9%)	74 (83.1%)	58 (65.2%)	82 (92.1%)
	Type 2 (n = 328)	210 (64.0%)	236 (72.0%)	272 (82.9%)	262 (79.9%)	302 (92.0%)
FMs	**Group 1** (n = 85)	51 (60.0%)	64 (75.3%)	70 (82.3%)	64 (75.3%)	78 (91.8%)
	Group 2 (n = 35)	18 (51.4%)	25 (71.4%)	30 (85.7%)	23 (65.7%)	31 (91.4%)
HCPs	**PCPs/GPs** (n = 68)	15 (22.1%)	32 (47.1%)	40 (58.8%)	26 (38.2%)	37 (54.4%)
	Specialists (n = 40)	13 (32.5%)	17 (42.5%)	18 (45.0%)	16 (40.0%)	23 (57.5%)
	NDOs (n = 119)	25 (21.0%)	50 (42.0%)	56 (47.1%)	40 (33.6%)	64 (53.8%)

PWD: person with diabetes; FM: family member; HCP: health care professional

Areas of improvement

The three study groups (PWD, FM and HCPs) were asked for their opinion about areas where they feel there was still a need for additional education to help people with diabetes in their community and society (Table 6). Earlier diagnosis and treatment of diabetes was the major area of concern for PWD and FMs – PWD type 1 – 92.1% (n = 82), PWD type 2 – 92.0% (n = 302); FMs type 1 – 91.8% (n = 78), FMs type 2 – 91.4% (n = 31) – whereas for HCPs was a less relevant area of concern – PCPs/GPs /FPs– 54.4% (n = 37); Hospital based specialists – 57.5% (n = 23); NDOs – 53.8% (n = 64). The same pattern of responses between PWD/FMs and HCPs was observed for all other areas for improvement assessed, with PWD/FMs reporting more concern (51% – 83% range of positive answers) and HCPs less concern (21% – 59% range of positive answers). The main areas for improvement identified by HCPs were: "Availability of diabetes self-management education" [PCPs/GPs – 67.6% (n = 46); Hospital based specialists – 60.0% (n = 24); NDOs – 54.6% (n = 65)]; "Availability of resources for psychological support for diabetes" [PCPs/GPs/FPs – 61.8% (n = 42); Hospital based specialists – 65.0% (n = 26); NDOs – 54.6% (n = 65)]; and "Planning and coordination of care for patients with multiple diseases" [PCPs/GPs/FPs – 60.3% (n = 41); Hospital based specialists – 45% (n = 18); NDOs – 57.1% (n = 68)].

DISCUSSION

In this study we have applied the DAWN2 protocol[10] to the Portuguese setting, addressing the wishes, needs, and attitudes of Portuguese diabetes patients, their relatives, and health professionals regarding the disease for the first time. The results obtained indicate that diabetes is associated with great physical and psychological burden for people with diabetes (PWD), with a negative impact on their physical health and emotional wellbeing. The psychological burden of diabetes was also clearly recognized in the original multinational DAWN2 study.[13] Also in line with the DAWN2 multinational study,[11,14] PWD in Portugal also reported high levels of diabetes-related distress. PWD's quality of life is affected by several factors which are associated with impaired disease self-management, and consequently, a gradual worsening of symptoms and disease-associated complications.[15,16] We believe that in order to mitigate this deterioration of PWD quality of life it is important to invest on continuous follow-up and evaluation of patients, with a particular focus on their psychological health.

There are few studies in the literature addressing the perceptions of family members of PWD. Nevertheless, the key role of FMs on disease management and support has been extensively highlighted by the data collected in the original DAWN2 multinational study.[11] In line with the original DAWN2 multinational study, in this study most PWD have recognized that their FMs often/always warn them if they are not managing diabetes properly and also take into consideration their difficulties in living with diabetes. Also in line with the original DAWN2 multinational study,[11] this study showed that diabetes is often a psychological burden for FMs, with a significant impact on their emotional wellbeing, due to their concerns and relevant role in caring for their relatives. Interestingly this burden for FMs may not be recognized by PWD. In fact, according to the DAWN2 USA data, PWD perceived support to be less frequent and less helpful than FMs. [17]

Regarding the perceptions of HCPs, most HCPs in this study recognized they have a significant role in influencing PWD in terms of the disease self-management. In addition, most endocrinologists and internal medicine specialists recognize the importance of addressing the emotional issues of the patient and believe they have an active role in terms of PWD advocacy. Patient perceptions can be inconsistent with those from healthcare professionals. Interestingly, both groups in this study recognized a mutual cooperative attitude in managing the disease. In fact, most patients have reported receiving help from HCPs in making plans to achieve their diabetes care goals, while most HCPs agreed that they frequently ask their patients for ideas, when making a plan for their diabetes care. In contrast with the observations of the DAWN2 multinational study,[18] Portuguese HCPs did not report being insufficiently prepared to provide diabetes self-management education to their patients.

In this study, we have also addressed the perceptions of PWD, FMs and HCPs concerning the organization of diabetes healthcare. PWD have reported to be generally satisfied

with the organization of their healthcare. However, several areas of improvement were mentioned, namely an earlier diagnosis and treatment of the disease, which implies an improvement of healthcare access, expansion of diabetes screening, and more health literacy programs, as previously discussed based on the data from DAWN2 study.[13] In addition, in our study PWD and FMs recognized that there is still some discrimination in society against the disease. Once again, we believe this discrimination is a consequence of inefficient literacy campaigns, which translates into low acceptance levels. Finally, PWD and FMs also mentioned logistic areas of improvement, namely: lack of places to buy healthy and affordable food, adapting workplaces to the disease management, and lack of safe places to make physical activity. According to HCPs, accessibility to diabetes self-management education programs was reported as an area for improvement, which is quite relevant, since, as previously described,[19] this kind of programs enables patients to gain important skills in managing their disease and live a healthier lifestyle, which translates into better clinical outcomes.

The DAWN2 study protocol has some limitations, namely concerning the difficulty to represent the DM population accurately, as previously recognized.[10] In particular, a great majority of PWD and FMs in this study were enrolled in the APDP headquarters, which mostly serves the Lisbon metropolitan area, the most populated area in Portugal, but still introducing a bias in the representativeness of our sample. In addition, we had difficulty in enrolling HCPs, particularly physicians, and to collect enough valid answers, as this group was not supported by an interviewer and, instead, self-administered the questionnaires. Our overall recruitment rate was lower than what is recommended by the DAWN2 protocol (767 *vs* 900 participants per country). Nevertheless, we managed to respect the recommended PWD:FM:HCP ratios: 54%:16%:30% in this study *vs* 55%:13%:31% in DAWN2 protocol.

Despite the DAWN2 study limitations, the generated multinational data was very useful to benchmark against different countries, enabling the identification of best practices and detection of areas for improvement.[20]

CONCLUSION

In this study, we have used for the first time in Portugal used the DAWN2 protocol to address the wishes, needs, and attitudes of Portuguese diabetes patients, their relatives, and healthcare professionals regarding the disease. The collected data suggest that diabetes has a negative impact on the physical health and emotional well-being of patients in Portugal, and is also a psychosocial burden for family members. In addition, this study has identified as main areas of improvement the earlier diagnosis and treatment of diabetes and diabetes self-management education. Altogether, the insights obtained with this study can guide the re-definition of priorities and pave the way for the design of better integrated healthcare strategies for diabetes management, reducing the physical and psychological burden of people living with diabetes.

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AUTHORS CONTRIBUTION

DMO: Data analysis and interpretation. definition of the design and structure of the article. Written document development and revisions.

LS, RTR, AC: Data analysis and interpretation; critical review of the manuscript. Approval of the final version. Agreement with all the developed topics, fidelity and precision of the delivered results.

SS, JMB, JFR: Significant contribution for the concept of the work and review of the paper structure. Approval of the final version. Agreement with all the developed topics, fidelity and precision of the delivered results.

MJA: Significant contribution as a nutritional educator in the analysis and interpretation of data. Approval of the final version. Agreement with all the developed topics, fidelity and precision of the delivered results.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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European Portuguese Language and Cultural Validation of the Chronic Obstructive Pulmonary Disease Assessment Test

Validação e Adaptação Cultural para o Português Europeu do Teste de Avaliação da Doença Pulmonar Obstrutiva Crónica

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ABSTRACT

Introduction: The chronic obstructive pulmonary disease assessment test (CAT) is a self-administered questionnaire that measures health-related quality of life. GOLD proposes using this questionnaire, since it provides thorough coverage of the impact of chronic obstructive pulmonary disease (COPD) on well-being. This questionnaire has been widely used in daily clinical practice in Portugal, but it lacks validation for European Portuguese. The aim of this study was to carry out the cultural adaptation and validation of the CAT questionnaire so that the most appropriate version can be made available to Portuguese researchers and clinicians.

Material and Methods: A cross-sectional descriptive study was performed involving 65 patients with COPD aged 40 years or older. CAT and the previously validated Portuguese-language version of the Clinical Questionnaire for COPD were applied between January 2019 and June 2019. The agreement between the two questionnaires was determined with Kappa agreement with a 95% confidence interval. Spearman correlation was used to find the correlation between two scores.

Results: The 65 patients included in the study were observed in a hospital-based pulmonology clinic [aged 68 ± 7 years; forced expiratory volume in 1 sec (FEV1) 49.86% ± 16.5% predicted]. CAT correlated significantly with all the domains and the overall score of the CCQ ($0.47 < r < 0.75$; $p < 0.001$). The bilingual patient interclass correlation coefficient was 0.922; Pearson's $r = 0.928$; $p < 0.001$. The Cronbach's alpha coefficient was 0.96 ($p < 0.001$).

Conclusion: The European Portuguese version of the COPD Assessment Test is a valid instrument for measurement of health-related quality of life in COPD patients. The use of validated questionnaires is of great importance since it generates reliable and reproducible evidence for use either in research or clinical practice.

Keywords: Portugal; Pulmonary Disease, Chronic Obstructive; Reproducibility of Results; Surveys and Questionnaires; Translating

RESUMO

Introdução: O teste de avaliação da doença pulmonar obstrutiva crónica (CAT) é um questionário autoaplicável que mede a qualidade de vida relacionada com a saúde. As normas internacionais GOLD propõem o uso deste questionário, uma vez que traduz o impacto da doença pulmonar obstrutiva crónica (DPOC) no bem-estar. Este questionário tem sido amplamente utilizado na prática clínica diária em Portugal, mas carece de validação para o português europeu. Assim, o objetivo deste estudo foi realizar a adaptação cultural e validação do questionário CAT para que a sua versão mais adequada possa ser disponibilizada a investigadores e clínicos portugueses.

Material e Métodos: Foi realizado um estudo transversal descritivo com 65 doentes com DPOC com 40 anos ou mais. O CAT e a versão em português previamente validada do questionário clínico para DPOC foram aplicados entre janeiro de 2019 e junho de 2019. A concordância entre os dois questionários foi determinada com o teste de concordância de Kappa com intervalo de confiança de 95%. A correlação de Spearman foi usada para avaliar a presença de uma correlação entre os dois *scores*.

Resultados: Os 65 doentes incluídos no estudo foram observados em consulta de pneumologia hospitalar [idade 68 ± 7 anos; volume expiratório máximo no 1º segundo (FEV1) 49,86% ± 16,5% do previsto]. O CAT correlacionou-se significativamente com todos os domínios e com a pontuação geral do CCQ ($0,47 < r < 0,75$; $p < 0,001$). O coeficiente de correlação interclasse de doentes bilíngues foi de 0,922; r de Pearson = 0,928; $p < 0,001$. O coeficiente alfa de Cronbach foi de 0,96 ($p < 0,001$).

Conclusão: A versão em português europeu do CAT é um instrumento válido para medir a qualidade de vida relacionada com a saúde em doentes com DPOC. A aplicação de questionários validados é fundamental, visto que gera evidência confiável e reprodutível para uso em ensaios clínicos ou na prática clínica.

Palavras-chave: Doença Pulmonar Obstrutiva Crónica; Inquéritos e Questionários; Portugal; Reprodutibilidade dos Testes; Tradução

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.[1] According to the WHO Global Health Estimates, COPD is currently the third leading cause of death in the world. A study in 2013 estimated the prevalence of COPD in the Lisbon region (Portugal) to be 14.2% in adults aged 40 or older, although it is often underdiagnosed.[2]

The diagnosis of COPD requires spirometry in subjects with a history of exposure to known risk factors (cigarette

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smoking and other environmental hazards) and symptoms such as dyspnea and/or chronic cough with sputum production.[3]

The management strategy for stable COPD should be predominantly based on the individualized assessment of symptoms and future risk of exacerbations.[1] One of the key issues in understanding the symptoms is to value them according to their impact on the health status of the patient. Therefore, when evaluating these individuals, we must obtain reliable and valid information on daily symptoms, activity limitation, and other manifestations of the disease. This is also important because symptom burden and health status increase the probability of future exacerbations.[4] A standardized patient-centered assessment tool covering key attributes of COPD facilitates information gathering on specific areas of greater severity to serve as a focal point for targeted management.[5]

According to the Global Iniciative for Chronic Obstructive Pulmonary Disease (GOLD), as compared with the modified British Medical Research Council (mMRC) dyspnea scale, the COPD assessment test (CAT) represents the impact of the disease on well-being to a greater extent and therefore should be used preferentially.[6] The CAT is a self-administered questionnaire that measures health-related quality of life and how it changes over time. It comprises eight items, each classified between 0 and 5, representing the increasing severity of the symptoms. The patients should mark the value that best describes their present situation. The total score ranges from 0 to 40, and it can be divided into four groups – 1) mild, 2) medium, 3) high, and 4) very high – representing the repercussions of the symptoms on the patient's life.[6] The Clinical Questionnaire for COPD (CCQ) is a clinical tool for evaluating the health status (symptomatology, functional status, and mental status) of people with COPD. The questionnaire comprises three domains and 10 items with an overall score: symptoms (four items), functional state (four items), and mental state (two items). Patients should answer the CCQ questions based on their experience in the last seven days on a Likert-based scale that assumes the following values: 0) never, 1) hardly ever, 2) a few times, 3) several times, 4) many times, 5) a great many times, and 6) almost all the time. The total score ranges from 0 to 60. The primary outcome measure of the CCQ is the mean total score (divided by 10 items), with higher scores representing worse health status and quality of life.[7] The CCQ was validated in 2012 for the Portuguese language.[7] The CAT has been validated for use in Brazilian Portuguese through a study that showed it to be a reproducible and reliable instrument for the assessment of COPD patients in the Brazilian population.[8] And even though this questionnaire has been widely used in daily clinical practice in Portugal, it lacks validation for European Portuguese. Thus, the aim of this study is to carry out the cultural adaptation and validation of the CAT questionnaire so that the most appropriate version can be made available to Portuguese researchers and clinicians.

MATERIAL AND METHODS

Translation

The Portuguese version of the CAT was obtained using a translation, back-translation, and comparison methodology carried out by a committee specially created for this purpose. The original version of CAT was translated into Portuguese by three independent translators, and three other independent translators performed the back-translation process. Five of the six translators recruited to find the final version of the questionnaire were from other institutions. The final versions were merged into one by a committee whose members were fluent in English, and it was compared with the original version. The committee did all the adjustments, converged them, and approved a unique and final European Portuguese language version (A.1). The equivalence between the two versions (English and European Portuguese) was also evaluated. Twelve bilingual individuals completed both versions, first the original version and the European Portuguese translation after a week. Correlations between the scores obtained with both versions were calculated.

Study design and data collection

This cross-sectional descriptive study was performed at the COPD clinic in Centro Hospitalar e Universitário de Coimbra between January 2019 and June 2019.

The inclusion criteria of the study were as follows: a) COPD diagnosis confirmed by spirometry [with a post-bronchodilator forced expiratory volume in 1 sec / forced vital capacity (FEV1/FVC) ratio < 0.7] at least six months before the study period; b) age of 40 years or above; c) attendance of the COPD consultations at the Centro Hospitalar e Universitário de Coimbra – Hospital Geral during the study period.

The following exclusion criteria were applied: a) history of medical conditions that could influence the dyspnea-related disability, such as asthma, active pulmonary tuberculosis, lung cancer, or pulmonary resection; b) non-pulmonary diseases considered to be incapacitating, severe, or difficult to control; c) infections or hospitalization within the last three months; d) history of COPD exacerbation (defined as an acute worsening of respiratory symptoms that results in additional therapy) within the last six weeks; e) medication change within the last four weeks; f) cognitive deterioration with inability to understand the questionnaire.

This protocol was approved by the competent human research ethics committee (Administração Regional de Saúde do Centro), and every patient was provided informed consent before being enrolled in the study.

The Portuguese version of CAT was given to the patient, who was instructed to read the descriptive statements in each item and select the number between 0 and 5 which best fits his or her symptoms. The CCQ for the Portuguese language, validated in 2012, was also applied to analyze the correlation between the two questionnaires.[7]

Patient demographics and disease related data (including FEV1% predicted and exacerbation history) were also obtained.

Statistical analysis

We summarized the characteristics of study populations using descriptive statistical methods with percentage, mean, and standard deviation (SD).

The agreement between these two questionnaires was determined with Kappa agreement with a 95% confidence interval. Spearman correlation was used to find the correlation between two scores. To evaluate the questionnaire's reliability, the Cronbach's alpha coefficient was determined. We performed all calculations using SPSS Statistics version 26®.

Outcome measures

The primary outcome was to determine the concordance of the GOLD classification while using these tools: the CAT and the CCQ. The cut-off points at CAT 10 and CCQ 2 were used to allocate patients into each GOLD classification.

RESULTS

The characteristics of the 65 participants of the study are represented in Table 1. Patients were predominantly male (86.15%) and had exposure to tobacco smoke (76.92%). This group was characterized by moderate to severe obstruction, as well as a small rate of exacerbations.

As represented in Table 2, most patients (58.46%) had CAT scores between 10 and 20. Comparing the results from both questionnaires, there were only three respondents (4.62%) who had a CAT score < 10 that had a CCQ score ≥ 2. On the other hand, 21.54% (n = 14) of the respondents who had a CAT score ≥ 10 had a CCQ score < 2 (Table 3).

Test-retest agreement was not performed, since the participants were enrolled in the setting of a medical appointment and were not hospitalized.

The CAT score correlated significantly with all the domains separately and the overall score of the CCQ ($0.47 < r < 0.75$; $p < 0.001$) (Table 4).

The mean administration time for the CAT questionnaire was 101 ± 1.1 seconds. The bilingual patient interclass correlation coefficient was 0.922; Pearson's r = 0.928; $p < 0.001$. The Cronbach's alpha coefficient was 0.96 ($p < 0.001$), showing high internal consistency, and the obtained kappa was 0.91 ($p < 0.001$) with a 95% confidence interval,

Table 1 – Demographic and disease-related characterization

Characteristics	**n**	**%**	**Mean** (± SD)
Age (years)			68 (7)
Sex (male)	56	86.15	
Weight (kg)			66.98 (9.55)
BMI (kg/m^2)			23.4 (3.9)
FEV$_1$% predicted			49.86 (16.5)
Gold A/B/C/D	23/26/7/9		
Smoking history	46	70.77	
Current smoker	4	6.15	
Exacerbations in the last 12 months			
0	28	43.08	
1	21	32.31	
≥ 2	16	24.62	

Table 2 – CAT and CCQ scores

Scores	**n**	**%**	**Mean** (SD)
CAT			15.17 (6.78)
Mild < 10	14	21.54	
Medium 10 - 20	38	58.46	
High 21 - 30	13	20.00	
Very high > 30	0	0	
CCQ total			2.13 (0.89)
CCQ Symptoms			2.33 (1.15)
CCQ Functional State			2.40 (1.20)
CCQ Mental State			1.20 (1.20)
Acceptable (CCQ < 1)	6	9.23	
Acceptable for moderate disease (1 ≤ CCQ < 2)	19	29.23	
Unstable – severely limited (2 ≤ CCQ < 3)	27	41.54	
Very unstable – very severely limited (CCQ ≥ 3)	13	20.00	

Table 3 – Categorization of patients in both scores

	CCQ < 2 (n/%)	**CCQ ≥ 2** (n/%)
CAT < 10 (n/%)	11/16.92	3/4.62
CAT ≥ 10 (n/%)	14/21.54	37/56.92

Table 4 – Correlation of CAT with CCQ

CCQ domains *vs* CAT	**r**	***p***
Symptoms CCQ *vs* CAT	0.62	< 0.001
Functional state CCQ *vs* CAT	0.64	< 0.001
Mental State CCQ *vs* CAT	0.47	< 0.001
CCQ Total *vs* CAT	0.75	< 0.001

which also shows excellent agreement. There were also no absent answers.

DISCUSSION

The CAT questionnaire correlated significantly with all the domains and the overall score of the CCQ questionnaire, showing that the translated version is valid. Also, the intraclass correlation coefficient and the Cronbach's alpha coefficient obtained showed the reproducibility and the reliability of this questionnaire.

Even though CAT is widely recommended for the evaluation of patients with COPD, we found no studies of validation and cultural adaptation of the Portuguese version of CAT.

The CCQ was chosen as the validation criterion for the Portuguese language version and cultural adaptation of CAT because it is an instrument with proven validity and is widely used in scientific research.[7] There is previous evidence that CAT and the CCQ are both measuring similar factors and can be used reliably and interchangeably.[9]

In the study concerning the development and first validation of CAT, internal consistency was excellent with Cronbach's alfa = 0.88, which is higher than the acceptable value of 0.70 and the correlation between the CAT and St George's Respiratory Questionnaire-C (SGRQ-C) in stable patients was very good (r = 0.8) and equally good (r = 0.78) in acute patients with an exacerbation.[5] Posterior adaptations and validations for other languages also showed high reliability and good correlation with other validated scores,[7,10,11] as demonstrated in our study.

According to GOLD, classifying COPD patients into four subgroups by considering symptoms and exacerbations allows the stratification of therapy and prognosis.[1] These two dimensions should also be assessed in the follow-up of these patients and are crucial for their ongoing management. In order to achieve this, symptomatic evaluation through validated scores such as CAT and mMRC is essential. Therefore, when treating these patients, individualization of therapy is a core concern, and this can only be accomplished by the correct assessment of symptom impact on COPD patients, which further strengthens this validation study.

On the other hand, even though CAT and mMRC are useful for clustering patients into groups with therapeutic and prognostic implications, these two scores evaluate different dimensions of symptoms in COPD patients.[12] Future studies should address this issue in order to allow physicians to choose the most suitable tool to assess each patient.

As this study was performed in a hospital outpatient clinic, it included mostly patients with moderate to severe airflow obstruction and with small rates of exacerbation. We believe that further validation studies should include larger and more representative samples, bearing in mind that an individualized approach is essential to reduce symptoms and exacerbations and improve health status.

An important limitation in this process of cultural validation and adaptation is the lack of test-retest assessment, given the clinical context in which the questionnaires were provided to patients. Despite this limitation, we believe that it is not a critical error in our methodology, considering all the other positive findings mentioned above. According to the type of study we conducted, we were unable to evaluate the responsiveness of the Portuguese-language version of the CAT in interventions such as pulmonary rehabilitation or bronchiectasis.[13] This may also be considered a limitation of the study. However, other studies have used the same approach,[14-17] and we have done so previously.[18,19] We also recognize that the sampling method is not entirely free of bias, even though there was always a great effort by everyone, and the patients included are patients who attend the clinic and who agreed to participate in the study.

The importance of the validation of this questionnaire in our language is the possibility to use a reliable tool in evaluating COPD patients in various scenarios from primary care to hospitalized patients. Previous studies performed have showed the utility of CAT in these two settings.[20,21]

The validation and cultural adaptation of CAT to patients based in Portugal is therefore of significant importance, and the present study showed this version of CAT to be valid, reproducible, and reliable questionnaire.

The administration of validated questionnaires is essential since it generates reliable and reproducible evidence for use in either research or clinical practice. Questionnaires that are validated for a specific population help to collect better quality data with high comparability increasing its credibility.[22] Since both therapeutic stratification and follow-up decisions are strongly based on symptom burden and this information is more objectively collected by validated symptom questionnaires, the future use of this European Portuguese version should improve care for these patients and boost evidence-based research in our country.

In the future we ought to continue the work in different settings and with further follow up, ensuring the stability over time and contexts of the Portuguese version of CAT.

CONCLUSION

The cultural adaptation of the European Portuguese version of the COPD Assessment test was validated by this study since this translated version correlated significantly with the CCQ and displayed feasibility and external validity

when compared with a traditional and previously validated instrument. We showed this version of CAT to be valid, reproducible, and reliable questionnaire. The lack of test-retest assessment was a limitation to consider since it would provide us the stability coefficient of this questionnaire, showing whether individuals responses would change over different time periods. Nevertheless, and considering all other findings, the European Portuguese version of the CAT is a valid instrument for measurement of health-related quality of life in COPD patients.

AUTHORS CONTRIBUTION

MPV: Data collection and treatment, manuscript outline, review and final approval

SR, CSC: Study design, review and correction of the manuscript, final approval.

JM, JC: Collection and treatment of data, review and correction of the manuscript, final approval.

CR: Manuscript review and correction, final approval

ARM: Statistical study. Review of the manuscript, final approval.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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The Patient Perspective Regarding Ambulatory Surgery: An Observational Study

A Perspetiva do Doente Sobre a Cirurgia em Regime de Ambulatório: Um Estudo Observacional

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Due to the advances in anesthetics and surgery, ambulatory surgery plays an increasingly important role. This regimen, despite showing several advantages, still instills fear in patients. The aim of this was to evaluate the level of knowledge and the perspective of patients regarding ambulatory surgery.

Material and Methods: A prospective study was carried out for two months in patients with pre-anesthetic consultation at a University Hospital Center. Demographic information, educational level, and previous ambulatory surgery were surveyed. Patients' level of knowledge about surgery, satisfaction, and the perceived advantages and fears regarding this regimen were evaluated. The analysis was performed with SPSS, and $p < 0.05$ was considered statistically significant.

Results: Two hundred and fifty-one patients were included. One hundred and twenty-eight (51%) patients disclosed having knowledge about ambulatory surgery. The main advantages perceived by patients were more peaceful recovery (44.7%), avoiding being surrounded by other patients (43.1%), and avoiding infection (37.2%). The main fears shown by patients were poor pain control (20.7%), having other health problems (13.1%), and poor control of nausea or vomiting (10%).

Conclusion: Patients may benefit from being more informed about the ambulatory surgical regimen in order to decrease their fears and increase their acceptance of the regimen. Providing more information to patients may result in increased satisfaction with this regimen.

Keywords: Ambulatory Surgical Procedures; Anesthesia; Patient Satisfaction

RESUMO

Introdução: Com os avanços observados a nível anestésico e cirúrgico, a cirurgia em regime de ambulatório tem cada vez mais expressão. Este regime, apesar das várias vantagens para os doentes, acarreta também vários receios. Os objetivos deste estudo foram avaliar o nível de conhecimento e a perspetiva dos doentes sobre a cirurgia em ambulatório.

Material e Métodos: Estudo prospetivo decorrido durante dois meses em doentes com consulta pré-anestésica num Centro Hospitalar Universitário. Foi inquirida informação demográfica, nível educacional e existência de cirurgia prévia em regime de ambulatório. Foram avaliados o nível de conhecimento dos doentes, a satisfação, as vantagens e receios relativos à cirurgia em regime de ambulatório. A análise foi feita com SPSS (v 27.0) e $p < 0,05$ foi considerado como estatisticamente significativo.

Resultados: Foram incluídos 251 doentes. Destes, 128 (51%) doentes demostraram ter conhecimento sobre a cirurgia de ambulatório. As principais vantagens percebidas pelos doentes foram ter uma recuperação mais sossegada (44,7%), evitar estar rodeado de outros doentes (43,1%) e evitar infeção (37,2%). Os principais receios mostrados pelos doentes foram o mau controlo da dor (20,7%) e de náuseas/vómitos (10%) e ter outros problemas de saúde (13,1%).

Conclusão: Os doentes poderão beneficiar de ser mais informados sobre o regime cirúrgico em ambulatório de forma a diminuir os seus receios e aumentar a sua satisfação. Investir na informação do doente poderá aumentar a aceitação do regime de ambulatório.

Palavras-chave: Anestesia; Procedimentos Cirúrgicos Ambulatórios; Satisfação do Doente

INTRODUCTION

Ambulatory surgery (day surgery) is defined as an elective surgical procedure where patients are admitted and discharged from the hospital in less than 24 hours, in proper facilities and safety conditions in accordance with current clinical practice.[1] Another important concept is the extended recovery patient, that the International Association of Ambulatory Surgery (IAAS) defined as "a patient treated in ambulatory surgery/procedure center/unit, free-standing or hospital-based, who requires extended recovery including an overnight stay, before discharge the following day".[2] Nevertheless, in our study, we particularly focused on patients who were discharged from the hospital within the same day.

In order to evaluate the impact and prevalence of ambulatory surgery worldwide, the IAAS started to carry out multinational surveys. In its first edition, in the 1990s, a high inter-country disparity was noted, with the prevalence rate of outpatient surgery ranging between 9.9% in Portugal, 21.9% in Italy, 30.2% in France, 66.7% in the Netherlands, and 78.5% in Denmark.[3] In later editions, the progressive growth of this surgical regimen was notorious.[4] In 2015, in a small article where Appleby highlights the economic benefits of outpatient surgery in the UK, he emphasizes that in this country, from 7% of the total number of surgeries in 1974, ambulatory surgery came to represent 78% in 2013.[5]

While still having a large growth potential, in Portugal, ambulatory surgery represents 66.1% of all elective

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surgery (data collected by the Annual Report on Access to the National Health Service from 2019).[6] This figure is highly promising and is expected to grow to the levels seen in Northern Europe, where ambulatory surgery accounted for 69% and 74% of all surgeries in Sweden and Denmark, respectively, in 2009.[7]

Ambulatory surgery is currently performed in patients who were previously required to stay at the hospital.[2] This is due to recent surgical and anesthetic techniques.[2,8] Moreover, this option is better suited to minimally invasive surgeries, which are being performed more often.[9] The attempt to reduce the costs of healthcare services combined with the cost-effectiveness of ambulatory surgery are two added reasons for this increase.[2]

Additionally, ambulatory surgery has brought several advantages to patients. It allows patients to recover in their home environment, with minimal disruption to their routines,[10-13] and it helps avoid medication-related problems that can arise from prolonged hospitalization.[10] It is also associated with less pain and lower thromboembolic risk derived from early ambulation,[12] as well as with lower infection rates mainly because of the shorter hospital stay[10,12] and with lower stress levels for the patients' relatives.[12]

Patient satisfaction after ambulatory surgery appears to be high, fulfilling most of their expectations.[11,13-15] Also, patients who undergo this type of surgery appear to prefer this option, with 97% of them claiming that they would choose ambulatory surgery again.[16]

However, despite the fact that ambulatory surgery appears to be a well-accepted procedure,[11,14] patients still have some concerns about potential risks, namely postoperative complications.[11] More specifically, patients fear poor pain management, being dependent on others for help, suffering from a fall, lack of sufficient support, and nausea, etc.[17] They also fear not having enough knowledge about rehabilitation,[11] as well as not having enough generic knowledge on ambulatory surgery.[18]

Considering that the paradigm of medicine and surgery is evolving from being disease-focused, to becoming more patient-centered,[18] it becomes crucial to understand the patient's perspective regarding the advantages and concerns of ambulatory surgery. With this data, we will be able to include the patients as active participants in the decision-making process of their care.[19] A higher level of patient education leads to better surgical outcomes, overall satisfaction, reduced anxiety levels, and increased patient well-being.[20,21] The widely known enhanced recovery after surgery (ERAS) has already confirmed these positive findings.[22]

Therefore, the aim of this study was to evaluate patients' knowledge and perspectives about the ambulatory surgery.

MATERIAL AND METHODS

After receiving approval from our institutional ethics committee, we performed a prospective study at the Ambulatory Surgery Department, with the duration of two months (estimated period, based on the number of surgeries in our center, to obtain a number of responses close to that reported by similar articles[11,14,17,23]). Patients older than 18 years that were proposed for ambulatory surgery were included. The data were collected before the assessment visit with the anesthesiologist. Exclusion criteria were: patient's refusal, non-autonomous patients, unlettered patients.

Each patient was given a questionnaire (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16494/Appendix_01.pdf), which they filled. The questionnaire was developed by a group of anesthesiologists based on relevant articles that focused on knowledge of this regimen,[11,17] perceptions about outpatient surgery and its risks and benefits,[11,16,17] and on patient satisfaction with this option.[11,14,16,23] The following variables were included in the questionnaire: demographic data, the highest level of education, and previous experience in ambulatory surgery. We evaluated patient perception about ambulatory surgery, including the level of knowledge of patients, patient satisfaction, and patient perceived advantages and concerns regarding this regimen. Patient consent was obtained.

All the data collected in this study were compiled and summarized with descriptive statistics. The results are presented as percentages or medians.

Demographic variables, as well as the answers to the questionnaire, are presented as percentages or absolute values. Statistical analysis was performed using SPSS software (v 27.0). An association was sought between the patient's ambulatory surgery-related knowledge and the level of education or previous exposure to ambulatory surgery. A chi-square test was used. A p-value < 0.05 was considered statistically significant.

RESULTS

Two hundred and fifty-one patients participated in this study.

Demographic data, education level, and a history of previous ambulatory surgery are shown in Table 1.

Table 1 – Demographic data: gender, age, education level, previous ambulatory surgery

Gender, n (%)	
Masculine	75 / 29.9
Feminine	158 / 62.9
Non-respondents	18; 7.2
Age (median; Q1; Q3)	47; 38; 55
Education level, n (%)	
Did not finish high school	131 (52.2)
High school	63 (25.1)
College education	39 (15.5)
Non-respondents	18 (7.2)
Previous ambulatory surgery, n (%)	
Yes	91 (36.3)
No	127 (50.6)
Non-respondents	33 (13.1)

Table 2 – Patient-related knowledge about ambulatory surgery

Ambulatory surgery is, n (%):	
- A surgery in which the patient is discharged in the first 24 hours after the surgical intervention	128 (51.0)
- Wrongly answered	83 (33.1)
- Non-respondents	40 (15.9)
All the patients included in the study	251
Ambulatory surgery is, n (%):	
- A surgery in which the patient is discharged in the first 24 hours after the surgical intervention	48 (52.7)
- Wrongly answered	31 (34.1)
- Non-respondents	12 (13.2)
Patients who had been previously operated in an ambulatory basis	91

Results regarding the ambulatory surgery-related knowledge are shown in Table 2.

When asked if they would like to be given more information about ambulatory surgery, the majority (60.2%) answered positively. Forty-one patients did not respond.

We asked patients who were previously operated on an outpatient basis about their experience regarding the information provided in that previous surgery. Seventy-seven (84.6%) patients claimed to have received all the information needed to feel safe. When asked if they would prefer to have stayed in the hospital for a longer period of time, 79 (86.8%) replied “no”. Regarding the two questions mentioned, two and three patients did not respond, respectively.

Concerning patient fears regarding ambulatory surgery, we can see from Table 3 that poor pain management was the most prevalent concern, having been mentioned by 20.7% of patients.

When asked about the possibility of being able contact a doctor promptly in case of doubt, the majority (81.3%) of patients said “yes”. Thirty-five patients did not respond.

As for the patient perspective regarding ambulatory surgery, the non-respondents were 52, with 94.5% of the patients who answered the question considering it as advantageous. The main advantages pointed out by these patients are summarized in Table 4. Concerning the most relevant advantages inherent to ambulatory surgery, 63.3% of patients pointed to the reduction of surgical waiting lists, 23.1% to reduced healthcare costs, 11.6% to reduced daily routine disruptions, and 8.8% to reduced nurse and medical workload. This is depicted in Table 5.

When questioned about the most relevant aspects to their satisfaction regarding ambulatory surgery, as we can see in Table 6, 131 (52.2%) patients selected the surgical outcome.

Lastly, a possible association between knowledge about ambulatory surgery and the general level of education, as well as between knowledge about ambulatory surgery and a previous exposure to ambulatory surgery, was addressed.

Table 3 – Patients’ concerns regarding ambulatory surgery

What do you fear most about ambulatory surgery?	n (%)
- Poor pain management	52 (20.7)
- Not being able to perform your personal hygiene	17 (6.8)
- Suffer a fall	9 (3.6)
- Not having enough support	16 (6.4)
- Manage medication	0 (0)
- Poor nausea and vomit management	25 (10)
- Not being able to change the bandage	16 (6.4)
- Having other health related complications	33 (13.1)
- Non-respondents	122 (48.6)

Table 4 – Patients’ perception regarding the personal advantages of ambulatory surgery

What is, for you, the main advantage of having a surgery on an ambulatory basis?	n (%)
- Avoiding infection	70 (37.2)
- Sleep better, at home	39 (20.7)
- Having a more peaceful recovery	84 (44.7)
- Avoiding being surrounded by other patients	81 (43.1)
- Eating tastier food, at home	18 (9.6)
- Avoiding parking related problems	5 (2.7)
- Non-respondents	5 (2.7)

Table 5 – Patients' perception regarding the inherent advantages of ambulatory surgery

In your opinion, what do you consider to be the biggest advantage of ambulatory surgery?	n (%)
- Reducing patient daily routine disruptions	29 (11.6)
- Reducing surgical waiting lists	159 (63.3)
- Reducing nurse and medical workload	22 (8.8)
- Reducing heath care costs	58 (23.1)
- Non-respondents	47 (18.7)

Table 6 – Patients´ perception regarding the most satisfactory aspects about ambulatory surgery

In your opinion, what matters the most to the satisfaction derived from ambulatory surgery?	n (%)
- Hospital environment	14 (5.6)
- Doctor-patient communication	50 (19.9)
- Agility of the hospital process	80 (31.9)
- Procedure outcome	131 (52.2)
- Non-respondents	49 (19.5)

Statistically significant differences were not observed for any of the variables (*p*-value = 0.099 and *p*-value = 0.934, respectively).

DISCUSSION

In this study, only 51% of the patients demonstrated a reasonable amount of knowledge about this regimen. This percentage overlapped when just the patients previously operated on this regimen were considered, with 52.7% answering correctly. These findings may reflect the participant's low level of formal education participants. Furthermore, as previously mentioned, despite the enormous growth of ambulatory surgery, in Portugal, it is still not very significant compared to other countries,[7] a fact that may help explain this lack of knowledge. The study by Meneghini *et al*[24] regarding outpatient arthroplasty found similar findings: only 54.5% of the patients included were aware of this surgical option.

In our sample, 84.6% of patients previously operated on an ambulatory basis reported having all the information necessary to feel safe, which is similar to the data presented by Harju[25] and McCloy *et al*.[26] Moreover, 86.8% of patients stated that they would not have stayed in the hospital longer, which is in line with the findings of the study by Weale *et al*,[27] where 90% of patients who were operated on an outpatient basis preferred this regimen. Also, in the study by Philip,[16] 97% of the sample stated that they would opt for the same regimen again. This translates into a high level of satisfaction regarding ambulatory surgery, not only due to the responses obtained but also due to the fact that patients tend to repeat this choice, which is in line with the available literature, where high levels of satisfaction are described.[11,13-16]

In our study, the surgical outcome, the agility of the hospital process, and the doctor-patient communication were the aspects observed as most relevant to patient satisfaction. This is consistent with the studies by Lemos *et al*,[14] which reported the final outcome and the clinical information as being statistically significant, with an odds ratio of 3.153 and 1.609, respectively. For Holland *et al*,[23] the clinical quality and safety, as well as courtesy and sensitivity, were the only dimensions of patient satisfaction that were statistically significant. Chung *et al*[15] showed that the doctor-patient quality of interaction is one of the most important predictors of patient satisfaction.

The majority (60.2%) of patients conveyed a desire for more information, which is in line with the previous literature. In the study by Otte,[13] patients stated a desire for more information regarding their surgery, surgical outcome, and recovery. Thus, it becomes advisable to create training initiatives in order to provide information about the peri-operative period to the patient.

Regarding the advantages perceived by the patient, s the reduction in infection rate the most prevalent in our study (37.2%) and the recovery comfort, which combines both having a more peaceful recovery (44.7%) and avoiding being surrounded by other patients (43.1%). These results are in line with the literature, wherein the studies by Adelani *et al*,[17] Meneghini *et al*,[24] and Evans *et al*[28] reported that avoidance of infection was one of the most common advantages. Furthermore, these studies reported prevalence rates of 57.3%, 72.8%, and 38.2%, respectively. Recovery comfort is emphasized in the study by Adelani *et al*[17] and Evans *et al*,[28] with prevalence rates of 42.7% and 73.4%, respectively. However, we observed some differences in the study by Adelani *et al*,[17] where avoiding being surrounded by other patients only ranks fifth, being mentioned by 18.8% of patients, whereas, in our study, this was one of the most prevalent advantages (43.1%).

In addition, the opinions of patients concerning the inherent advantages of ambulatory surgery were also evaluated, where reducing surgical waiting lists (63.3%) and reducing health care costs (23.1%) were the most perceived. These results show the opposite of what was found in the study by Yu *et al*,[11] where the economic aspects were the least valued (43%), whereas the social and the convenience aspects were mentioned by 87% and 60%, respectively. Also, in the studies by Otte[13] and Read,[29] the minimal disruption in

the lives of patients and their families was the most valued advantage.

Although patients acknowledge that ambulatory surgery has certain advantages, there is still a strong belief that the economic benefits are the main driving force of this practice. Comfort and healthcare improvement aspects are not recognized to be equally important. Thus, it is necessary to work towards improving the communication with the patient, explaining all the aspects in which this regimen proves to be beneficial and not just the economic benefits.

Patients perceive advantages in this regimen but also have some fears. These were also studied. The most frequently mentioned were poor pain management (20.7%), followed by fear of having other health-related problems, and poor management of nausea and vomiting. However, the response rate of this question was only 51.4%, which leaves us in doubt as to whether the lack of answers was due to patients' lack of concern or whether they simply did not answer the question, indicating that, perhaps, the question was poorly understood. Our observations are in line with the available literature where the majority (75%) of patients mentioned being afraid of suffering some postoperative complication.[11] In the study by Jenkins *et al*,[30] concerning postoperative complications in an ambulatory setting, pain, nausea, and vomiting were mentioned in a 1 - 10 ranking scale, with a 9 and an 8, respectively, being amongst the most disturbing complications. Also, in the study by Adelani *et al*,[17] the fear of feeling pain is referred to as the most prevalent (54.8%). Despite the efforts, pain, nausea, and vomiting are concerns that are often mentioned by patients, which demonstrates there are real and well-founded fears, with these being the most frequently reported adverse events in the literature regarding the postoperative period.[31-33] A plausible strategy might be to provide easy access to dedicated healthcare professionals so that patients can clarify their doubts. This strategy seems to be well accepted by patients, with most being in favor (81.3%).

This study has several limitations. The population under study was taken from the pre-anesthetic consultation. This may have led to more informed patients, both in anesthesia and in surgery, in contrast with the general population. The poor or incomplete filling of the questionnaire may have led to answers that are not representative of the reality of individual patients. Moreover, the low level of education of the majority of the participants may have led to more difficulties regarding the interpretation of the questionnaire. The use of a questionnaire as the means to obtain the data may have led to a misinterpretation of the questions, as well as to a limitation in terms of the answers obtained, unlike in an interview. The fact that the data originated from the same center may lead to responses that do not translate the national reality since there may be differences at the population level, as well as in the pre-operative education provided by the different centers.

Regarding the incomplete filling of the questionnaire, we admit that some patients might have felt inhibited due to their lack of knowledge about the topic. If this is the case, the results obtained may be overestimated. On the other hand, the place where it was delivered (in the consultation waiting room) could potentially have made it difficult for some patients to fill out the questionnaire. Finally, we admit that the questionnaire was not understood by some patients given the low educational level of the participants.

CONCLUSION

There may be a big gap in patient knowledge regarding ambulatory surgery, with only about half of patients in this study responding correctly. According to patients, the main advantages of ambulatory surgery include a peaceful recovery, avoiding being surrounded by other patients, and avoiding infection. Despite the high level of satisfaction found, patients reveal several fears about this regimen (poor pain control, having other health problems and poor control of nausea or vomiting being the most common), as well as a desire for more information. Therefore, it is important to provide more information and further integrate patients while meeting their needs. Satisfaction, acceptance, and in the end, the success of this regimen rely entirely on the patient. Thus, according to the new paradigm of medicine, a more patient-centered approach where the patient has a more active role in the decision process is needed.[13] We must look for new approaches to further improve the level of satisfaction and reduce the perceived fears, so that a higher acceptance rate of this regimen can be achieved.

AUTHORS CONTRIBUTION

MS: Design of the work and questionnaire, draft of the manuscript.

JS: Data acquisition, draft of the manuscript, statistics analysis.

JN: Design of the questionnaire, data processing,

FO: Data processing, statistics analysis.

EC: Draft of the questionnaire, critical review of the paper.

JM: Design of the work and questionnaire, critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Improving Awareness about Patient Blood Management in Portugal: A Call for Action Arising from a Delphi Panel

Melhorar a Consciencialização sobre Patient Blood Management: Um Repto de Ação a Partir de um Painel de Delphi

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Anaemia and iron deficiency are associated with increased mortality and poor surgical outcomes. Consensus in their definitions is expected to optimize their management, which is encompassed by patient blood management, providing patient-centred care while improving patient safety and clinical outcomes. Patient blood management implementation is even more relevant in contingency times and faces barriers due to lack of standardization, among others. The aim is to establish a consensus on these diagnoses and implement patient blood management principles in clinical practice in Portugal.

Material and Methods: Eight experts in Transfusion Medicine, Haematology, Anaesthesiology, Internal Medicine, and Obstetrics/Gynaecology were assembled; a focus group was conducted, defining 33 statements. A Delphi panel was conducted, with experts from the clinical specialities named above as well as from General Surgery, Urology, and Orthopaedics.

Results: The Delphi panel's rounds had 70 (Round 1) and 46 (Round 2) respondents. Specialists were consensual in only two statements, on the existence of a preoperative patient blood management consultation for candidates to elective surgeries in which the use of blood derivatives is anticipated and, on the importance of the correction of postoperative anaemia and iron deficiency. Of the remaining 31 statements, 27 reached high agreement or disagreement by the respondents.

Conclusion: Consensus was reached in only two (6%) of the 33 statements. There was a consensual agreement on the relevance of establishing patient blood management as the standard of care and of valuing preoperative and postoperative patient blood management interventions. Nevertheless, our results point to the lack of awareness regarding patient blood management principles – which could result in better postoperative outcomes, shorter hospitalizations, reduced costs and increased availability of beds. Training and literacy initiatives could help further implement patient blood management standards in Portuguese hospitals.

Keywords: Anemia; Anemia, Iron-Deficiency; Biomarkers/blood; Blood Transfusion; Consensus; Iron Deficiencies; Perioperative Care

RESUMO

Introdução: A anemia e ferropenia estão associadas a um aumento da mortalidade e a piores resultados no período pós-operatório. Consensualizar as suas definições permitirá otimizar a sua gestão. O *patient blood management* engloba essa gestão, com relevo acrescido em situações de contingência, focado nos cuidados centrados no doente e na melhoria da segurança e dos *outcomes*. As barreiras à implementação de princípios *patient blood management* prendem-se, entre outras, com falta de padronização. Pretende-se estabelecer um consenso sobre estes diagnósticos e implementação de *patient blood management* na prática clínica em Portugal.

Material e Métodos: Foram reunidos oito especialistas em Imuno-hemoterapia, Hematologia Clínica, Anestesiologia, Medicina Interna e Obstetrícia/ Ginecologia. Foi realizado um *focus group*, onde foram definidas 33 afirmações. Além disso, foi realizado um painel Delphi, com especialistas das áreas mencionadas acima, assim como de Cirurgia Geral, Urologia e Ortopedia.

Resultados: As duas rondas do painel Delphi tiveram, respetivamente, 70 e 46 respondedores. Estes foram consensuais em apenas duas afirmações, na existência de consulta pré-operatória de *patient blood management* para os candidatos a cirurgias eletivas em que se antecipa o uso de hemoderivados e, na importância da correção da anemia e ferropenia pós-operatórias. Das 31 afirmações restantes, 27 atingiram alta concordância ou discordância pelos respondentes.

Conclusão: Foi alcançado consenso em apenas duas (6%) das 33 afirmações. Houve consenso sobre a relevância de estabelecer o *patient blood management* como *standard of care* e a valorização das intervenções de *patient blood management* pré e pós-operatórias. No entanto, os resultados indiciam falta de consciencialização sobre os princípios de *patient blood management* – que poderiam levar a melhores resultados pós-operatórios, com redução do tempo de hospitalização e dos custos e maior disponibilidade de camas. Iniciativas de formação e literacia poderiam ajudar a uma melhor implementação dos princípios de *patient blood management* nos hospitais portugueses.

Palavras-chave: Anemia; Anemia por Deficiência de Ferro; Biomarcadores/sangue; Consenso; Cuidados Perioperatórios; Deficiências de Ferro; Transfusão de Sangue

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INTRODUCTION

Anaemia is defined as haemoglobin levels below the accepted lower level of the normal range,[1] set at 12 g/dL in women and 13 g/dL in men by the World Health Organization (WHO).[2] Nonetheless, these reference values have been challenged[3] and there is an urge to establish suitable thresholds and to define anaemia while ensuring its adequate diagnosis and management.[4] Furthermore, anaemia has been independently associated with increased morbidity, mortality, and poorer outcomes in a variety of disorders.[5,6]

Regarding iron deficiency, which is very common in the general population, no absolute consensus exists in terms of which biomarkers should be used for assessing the human iron status.[7] This is of particular relevance due to its frequent coexistence with anaemia, as well as its independent association with increased mortality.[8] Additionally, both anaemia and iron deficiency are more frequent in older age. Given that the Portuguese population is ageing, that probably results in more surgeries for patients with anaemia or iron deficiency.

Patient blood management (PBM) consists, according to the Society for the Advancement of Blood Management, in the proper and timely application of evidence-based concepts designed to maintain haemoglobin concentration, optimize haemostasis, and minimize blood loss – in order to improve patient outcomes.[9] This innovative multidisciplinary approach encompasses, in its broadness, the management of perioperative anaemia and iron deficiency.[10]

The incorporation of PBM principles into clinical practice and hospital-based processes is linked with improvements in patient safety and clinical outcomes,[11,12] in order to provide patient-centred care. These principles are even more relevant in contingency times, in which the third pillar of PBM (harness and optimize physiological reserve of anaemia) and its restrictive transfusion strategies[13] are relevant. Moreover, a meta-analysis indicated that PBM may be associated with a potential decrease in post-operative complications, when compared with control management, therefore highlighting the potential cost-effectiveness of its implementation in daily practice.[14] Nevertheless, implementation of PBM has not been widespread due to specific barriers such as the lack of awareness of the new standard operating procedures, and that many hospitals still need guidance to implement PBM – which ought to be the standard of care – in clinical routine.[10,15]

The aim of this study was to establish a consensus through a Delphi panel on the diagnosis of anaemia and iron deficiency, and on the implementation of PBM principles in clinical practice, by Portuguese medical experts in Transfusion Medicine, Haematology, Anaesthesiology, Internal Medicine, Obstetrics and Gynaecology, General Surgery, Urology, and Orthopaedics.

MATERIAL AND METHODS

The main purpose of the study was to assess the agreement level amongst medical specialists, regarding topic A – Anaemia and iron deficiency definitions; topic B – Patient blood management (PBM); and topic C – Follow-up of post-operative patients.

A group of eight medical experts in Transfusion Medicine, Haematology, Anaesthesiology, Internal Medicine, and Obstetrics and Gynaecology was assembled, and a focus group was conducted. The participants of the focus group were selected by invitation, and the meeting was conducted by a physician who did not intervene in the discussion. In this focus group, 33 statements concerning the above-mentioned topics were agreed upon (Table 1).

The conduct of a two-round Delphi Panel followed the statement setting phase. The Delphi panel method aims at reaching consensus on a given subject according to the opinion of experts through a multistage process of interactive rounds.[16] Its application is deemed as particularly useful in approaching complex, large, and multidisciplinary issues,[17] such as the topics covered by this study.

Round 1

The focus group participants were asked to reply to an anonymized online questionnaire sent by e-mail. They were equally invited to send the questionnaire's web-link to approximately twenty other medical experts working in their field (Transfusion Medicine, Haematology, Anaesthesiology, Internal Medicine, and Obstetrics and Gynaecology), as well as in General Surgery, Urology, and Orthopaedics. All participants were asked to categorize the 33 statements, presented in a randomized order, using a 4-point Likert scale: fully disagree; disagree; agree; fully agree.

The target response rate for round 1 was set at 50 respondents, and the consensus agreement level was set at 70%: all statements with at least 70% of responses "fully agree" or "fully disagree" were considered as consensual. The statements not reaching this consensus agreement level were subsequently selected to be include in an additional stage – Round 2.

Round 2

The experts who had participated in the first round were then asked to reply to another anonymized online questionnaire sent by e-mail, and the aim was to categorize the statements which failed to reach a consensus in round 1, using the same 4-point Likert scale.

The target response rate for round 2 was set at 30 respondents, and the consensus agreement level was set at 70%: all statements with at least 70% of responses "fully agree" or "fully disagree" were considered as consensual. All statements reaching above 70% in terms of combined agreement (i.e., "agree" and "fully agree") or disagreement (i.e., "disagree" and "fully disagree"), were classified as "highly agreed" upon.

RESULTS

Round 1

Consistent answers from 70 participants were obtained

Table 1 – Statements for the consensus process – round 1

A. Anaemia and iron deficiency	
A1	The World Health Organization (WHO) definition of anaemia is the most suitable. [Hb < 12.0 g/dL, women; Hb < 13.0 g/dL, men]
A2	In clinical practice the World Health Organization (WHO) definition of anaemia in not generally adopted.
A3	I define iron deficiency as ferritin below 30 ng/mL.
A4	I define iron deficiency as transferrin saturation ratio below 20%.
A5	To define iron deficiency, it is necessary to use ferritin levels together with the transferrin saturation ratio.
A6	The clinical and physiological contexts are of central importance to define iron deficiency.
A7	The definition of anaemia is different in the postoperative context.
A8	In the postoperative period a haemoglobin level of 10 g/dL does not imply any intervention.
A9	It is expectable for ferritin values to be altered after surgery.
A10	Ferritin is a good iron deficiency marker after surgery.
B. Patient blood management – PBM	
B1	A preoperative PBM medical appointment must exist only when addressing major surgeries.
B2	A preoperative PBM medical appointment must exist for all patients who are candidates to elective surgeries in which blood products are expected to be used.
B3	A preoperative PBM medical appointment must exist to all patients with anaemia candidates to elective surgeries.
B4	A preoperative PBM medical appointment must exist for all patients who are major surgery candidates.
B5	A preoperative PBM medical appointment must exist only when intraoperative blood losses above 500 mL are anticipated.
B6	A preoperative PBM medical appointment must exist only when addressing major surgeries.
B7	The preoperative hematologic assessment cannot be performed by the General Practitioner.
B8	The preoperative evaluation should include the reticulocytes' evaluation.
B9	In a patient with anaemia or iron deficiency which was documented the day before surgery there is no need to start preoperative treatment.
B10	Transfusion of red cell concentrates is the best strategy to treat anaemia in the immediate postoperative period (48 hours).
B11	It is mandatory to postpone elective surgeries of anaemic patients who have started anaemia correction in the preoperative period.
B12	In the postoperative period the evaluation of Complete Blood Count (CBC), ferritin, and transferrin saturation should be performed as soon as possible after surgery.
B13	In patients with stable volaemia the evaluation of CBC, ferritin, and transferrin saturation should be performed 12 to 24 hours after surgery.
B14	In the postoperative period the evaluation of CBC, ferritin, and transferrin saturation should be performed in all patients with anaemia (preoperative or postoperative) before hospital discharge.
B15	Postoperative clinical instability of patients in PBM programs do not change the timings to evaluate CBC, ferritin, and transferrin saturation.
B16	After surgery, the CBC should not include reticulocytes.
B17	After surgery it is equally important to correct anaemia and iron deficiency.
B18	The preferred treatment for anaemia in the postoperative period is transfusion of red cell concentrates.
B19	In the postoperative period iron deficiency without anaemia should not be treated.
B20	Erythropoiesis stimulant agents have no place in anaemia's postoperative correction.
C. Postoperative follow-up	
C1	A stable patient with controlled anaemia at the date of hospital discharge does not require subsequent follow-up.
C2	After hospital discharge the postoperative hematologic assessment should be conducted by the General Practitioner.
C3	At the postoperative 30 days revaluation, the surgeon should re-evaluate the CBC, ferritin, and transferrin saturation.

in the first round, which was above the target response rate previously established (50 respondents). The response rate was 100% for all statements.

None of the 33 sentences obtained consensus level in the first round. For this reason, all the sentences were transposed to the second stage of consultation - round 2.

Round 2

Consistent answers from 46 participants were obtained in the second round, which was equally above the target response established (30 respondents). Again, the response rate was 100% for all statements.

A consensus level was obtained for two sentences. Considering combined levels of agreement (i.e., "agree"

and “fully agree”) or disagreement (i.e., “disagree” and “fully disagree”), 27 statements were classified as highly agreed upon. The remaining four sentences were disregarded.

The obtained results are summarized in Table 2.

The specialists were consensual (i.e., more than 70% concordance) regarding [B2] “a preoperative PBM (Patient Blood Management) medical appointment must exist for all patients who are candidates to elective surgeries in which blood products are expected to be used” (71.7%) and that [B17] “after surgery it is equally important to correct anaemia and iron deficiency” (76.1%).

More than 90% of the participants agreed or fully agreed

Table 2 – Answers to the second stage of the consensus process - round 2

Reference number	Sentence
A1	The World Health Organization (WHO) definition of anaemia is the most suitable. [Hb < 12.0 g/dL, women; Hb < 13.0 g/dL, men]
A2	In clinical practice the World Health Organization (WHO) definition of anaemia in not generally adopted. [Hb < 12.0 g/dL, women; Hb < 13.0 g/dL, men]
A3	I define iron deficiency as ferritin below 30 ng/mL.
A4	I define iron deficiency as transferrin saturation ratio below 20%.
A5	To define iron deficiency, it is necessary to use ferritin levels together with the transferrin saturation ratio.
A6	The clinical and physiological contexts are of central importance to define iron deficiency.
A7	The definition of anaemia is different in the postoperative context.
A8	In the postoperative period a haemoglobin level of 10 g/dL does not imply any intervention.
A9	It is expectable for ferritin values to be altered after surgery.
A10	Ferritin is a good iron deficiency marker after surgery.
B1	A preoperative PBM medical appointment must exist only when addressing major surgeries.
B2	A preoperative PBM medical appointment must exist for all patients who are candidates to elective surgeries in which blood products are expected to be used.
B3	A preoperative PBM medical appointment must exist to all patients with anaemia candidates to elective surgeries.
B4	A preoperative PBM medical appointment must exist for all patients who are major surgery candidates.
B5	A preoperative PBM medical appointment must exist only when intraoperative blood losses above 500 mL are anticipated.
B6	A preoperative PBM medical appointment must exist only when addressing major surgeries.
B7	The preoperative hematologic assessment cannot be performed by the General Practitioner.
B8	The preoperative evaluation should include the reticulocytes’ evaluation.
B9	In a patient with anaemia or iron deficiency which was documented the day before surgery there is no need to start preoperative treatment.
B10	Transfusion of red cell concentrates is the best strategy to treat anaemia in the immediate postoperative period (48 hours).
B11	It is mandatory to postpone elective surgeries of anaemic patients who have started anaemia correction in the preoperative period.
B12	In the postoperative period the evaluation of CBC, ferritin, and transferrin saturation should be performed as soon as possible after surgery.
B13	In patients with stable volaemia the evaluation of CBC, ferritin, and transferrin saturation should be performed 12 to 24 hours after surgery.
B14	In the postoperative period the evaluation of CBC, ferritin, and transferrin saturation should be performed in all patients with anaemia (preoperative or postoperative) before hospital discharge.
B15	Postoperative clinical instability of patients in PBM programs do not change the timings to evaluate CBC, ferritin, and transferrin saturation.
B16	After surgery, the CBC should not include reticulocytes.
B17	After surgery it is equally important to correct anaemia and iron deficiency.
B18	The preferred treatment for anaemia in the postoperative period is transfusion of red cell concentrates.
B19	In the postoperative period iron deficiency without anaemia should not be treated.
B20	Erythropoiesis stimulant agents have no place in anaemia’s postoperative correction.
C1	A stable patient with controlled anaemia at the date of hospital discharge does not require subsequent follow-up.
C2	After hospital discharge the postoperative hematologic assessment should be conducted by the General Practitioner.
C3	At the postoperative 30 days revaluation, the surgeon should re-evaluate the CBC, ferritin, and transferrin saturation.

■: consensus “Fully agree”; ■: consensus combined levels “Agree” and “Fully agree”; ■: consensus combined levels “Disagree” and “Fully disagree”; ■: lack of consensus
PBM: patient blood management; CBC: complete blood count; FD: fully disagree; D: disagree: A: agree; FA: fully agree

about: [A6] "the clinical and physiological contexts are of central importance to define iron deficiency" (95.7%); [A9] "it is expectable for ferritin values to be altered after surgery" (91.3%); [B3] "a preoperative PBM medical appointment must be offered to all patients with anaemia, candidates for elective surgeries" (91.3%). Concomitantly, more than 90% of the participants disagreed or fully disagreed that: [B9] "in a patient with anaemia or iron deficiency which was documented the day before surgery there is no need to start preoperative treatment" (93.5%); [B18] "the preferred treatment for anaemia in the postoperative period is transfusion of red cell concentrates" (93.5%); [B19] "in the postoperative period iron deficiency without anaemia should not be treated" (95.7%).

D + FD (%)	FD (%)	D (%)	A (%)	FA (%)	A + FA (%)	Consensus	Agreement
19.6	2.2	17.4	60.9	19.6	80.4	-	x
43.5	6.5	37.0	39.1	17.4	56.5	-	-
13.0	2.2	10.9	43.5	43.5	87.0	-	x
21.7	4.4	17.4	45.7	32.6	78.3	-	x
15.2	2.2	13.0	34.8	50.0	84.8	-	x
4.3	2.2	2.2	41.3	54.4	95.7	-	x
76.1	32.6	43.5	19.6	4.4	23.9	-	x
73.9	23.9	50.0	21.7	4.4	26.1	-	x
8.7	0.0	8.7	41.3	50.0	91.3	-	x
76.1	32.6	43.5	21.7	2.2	23.9	-	x
34.8	13.0	21.7	37.0	28.3	65.2	-	-
2.2	0.0	2.2	26.1	71.7	97.8	x	-
8.7	0.0	8.7	23.9	67.4	91.3	-	x
17.4	2.2	15.2	30.4	52.2	82.6	-	x
78.3	30.4	47.8	17.4	4.4	21.7	-	x
78.3	32.6	45.7	19.6	2.2	21.7	-	x
71.7	23.9	47.8	17.4	10.9	28.3	-	x
15.2	0.0	15.2	50.0	34.8	84.8	-	x
93.5	69.6	23.9	6.5	0.0	6.5	-	x
84.8	32.6	52.2	13.0	2.2	15.2	-	x
71.7	19.6	52.2	17.4	10.9	28.3	-	x
50.0	2.2	47.8	39.1	10.9	50.0	-	-
28.3	2.2	26.1	56.5	15.2	71.7	-	x
10.9	0.0	10.9	52.2	37.0	89.1	-	x
82.6	28.3	54.4	17.4	0.0	17.4	-	x
87.0	39.1	47.8	13.0	0.0	13.0	-	x
2.2	0.0	2.2	21.7	76.1	97.8	x	-
93.5	56.5	37.0	6.5	0.0	6.5	-	x
95.7	60.9	34.8	4.4	0.0	4.4	-	x
80.4	23.9	56.5	15.2	4.4	19.6	-	x
87.0	30.4	56.5	10.9	2.2	13.0	-	x
41.3	2.2	39.1	52.2	6.5	58.7	-	-
15.2	2.2	13.0	41.3	43.5	84.8	-	x

At least 80% of the experts agreed or fully agreed in [A1] "the World Health Organization (WHO) definition of anaemia is the most suitable" (80.4%); [A3] "[they] define iron deficiency as ferritin below 30 ng/mL" (87%); [A5] "to define iron deficiency, it is necessary to use ferritin levels along with the transferrin saturation ratio" (84.8%); [B4] "a preoperative PBM medical appointment must be offered to all patients who are major surgery candidates" (82.6%); [B8] "the preoperative evaluation should include a reticulocyte count" (84.8%); [B14] "in the postoperative period the evaluation of Complete Blood Count (CBC), ferritin, and transferrin saturation should be performed in all patients with anaemia (preoperative or postoperative), before hospital discharge" (89.1%); [C3] "at the postoperative 30 days follow-up, the surgeon should re-evaluate the CBC, ferritin, and transferrin saturation" (84.8%). Likewise, at least 80% of the experts disagreed or fully disagreed that: [B10] "transfusion of red cell concentrates is the best strategy to treat anaemia in the immediate postoperative period (48 hours)" (84.8%); [B15] "postoperative clinical instability of patients in PBM programs do not change the timings to evaluate CBC, ferritin, and transferrin saturation" (82.6%); [B16] "after surgery, the CBC should not include a reticulocyte count" (87%); [B20] "erythropoiesis stimulant agents have no place in the postoperative correction of anaemia" (80.4%); [C1] "a stable patient with controlled anaemia at the date of hospital discharge does not require subsequent follow-up" (87%).

Finally, 70% or more of the respondents agreed or highly agreed in: [A4] "[they] define iron deficiency as transferrin saturation ratio below 20%" (78.3%); [B13] "in patients with stable volaemia the evaluation of CBC, ferritin, and transferrin saturation should be performed 12 to 24 hours after surgery" (71.7%). Similarly, 70% or more of the respondents disagreed or highly disagreed that: [A7] "the definition of anaemia is different in the postoperative context" (76.1%); [A8] "in the postoperative period a haemoglobin level of 10 g/dL does not imply any intervention" (73.9%); [A10] "ferritin is a good iron deficiency marker after surgery" (76.1%); [B5] "a preoperative PBM medical appointment must exist only when intraoperative blood losses above 500 mL are anticipated" (78.3%); [B6] "a preoperative PBM medical appointment must exist only when addressing major surgeries" (78.3%); [B7] "the preoperative haematological assessment cannot be performed by the General Practitioner / Family Physician" (71.7%); [B11] "it is mandatory to postpone elective surgeries of anaemic patients who have started anaemia correction in the preoperative period" (71.7%).

No consensus or agreement level was reached regarding the WHO definition of anaemia not being generally adopted in clinical practice, that a preoperative PBM medical appointment must exist only when addressing major surgeries, that the evaluation of CBC, ferritin, and transferrin saturation index should be performed as soon as possible after surgery, and that after hospital discharge the postoperative hematologic assessment should be conducted by the General Practitioner / Family Physician.

DISCUSSION

The aim of this study was to establish a consensus through a Delphi Panel on the diagnosis of anaemia and iron deficiency and on the implementation of PBM principles in clinical practice, which was only partially achieved. Consensus level was achieved for only two of the 33 statements included in the panel (6%) - the lack of consensus on this topic reinforces the need for awareness-raising training programs in this area and the implementation of PBM programmes.[18,19] Moreover, a high agreement level was reached for 27 statements (82%). Even though these results signal convergent perspectives from a broad range of medical specialties, they equally highlight the lack of awareness regarding PBM principles – which would allow better postoperative outcomes and minimization of other interventions.

The EMPIRE study, a population-based, cross-sectional study, estimated the prevalence of anaemia in Portugal as 19.9%, with 84% of cases previously undiagnosed.[20] This data also reinforces the need to conduct additional studies at the national level, given the epidemiology and prevalence of anaemia, and the implications it may have for the population. Apart from the established need for additional research and international consensus,[21] training and literacy initiatives could help further implement PBM standards in Portuguese hospitals.

The experts established as consensual that: PBM medical appointments must be offered to all patients who are candidates for elective surgeries in which blood products are expected to be used, and after surgery, it is equally important to correct anaemia and iron deficiency. These recommendations are in line with other studies, which have recognized the need for evidence-based approaches, with PBM activities being included in the preoperative, perioperative and postoperative routines, in all surgical units.[5] Furthermore, the postoperative treatment of anaemia and iron deficiency has been acknowledged as relevant in the literature, and linked with better postoperative outcomes, as well as improvements in patient performance and quality of life.[22]

In terms of anaemia and iron deficiency (Topic A), the respondents agreed on the WHO's definition of anaemia as being the most suitable, not considering it to be different in the postoperative context. Additionally, they disagreed that haemoglobin levels of 10 g/dL after surgery will not imply an intervention. As for the definition of anaemia (although bearing in mind that it may not translate into specific clinical approaches to given patients or haemoglobin levels), these findings are mirrored by other studies in which the WHO reference standards have indeed been commonly used.[11,23,24]

About iron deficiency, the experts agreed about the need of using ferritin levels (below 30 ng/mL) as well as the transferrin saturation ratio (below 20%). Additionally, the clinical and physiological contexts were agreed as being of central importance to the definition of iron deficiency. There is no full international consensus on biomarkers for the assessment of the iron status, since the diagnostic accuracy

of iron deficiency depends on its selection.[7] However, the panel's agreement is aligned with other studies on this matter, namely, in terms of the aforementioned reference levels and the multifactorial definition of iron deficiency.[3,8,25,26] Finally, the experts agreed that it is expected that for ferritin levels change after surgery, due to the elevation of ferritin levels as part of the postoperative acute phase inflammatory response.[27] It was agreed that ferritin a is not a good iron deficiency marker in the period after surgery.

Regarding patient blood management (Topic B), the clinicians agreed that all patients with anaemia who are candidates for elective surgery should have a preoperative PBM medical appointment, as well as all patients who are major surgery candidates. Conversely, combined levels of disagreement above the established threshold were reached for statements arguing that: preoperative PBM medical appointments should only be available when intraoperative blood losses above 500 mL are anticipated; preoperative PBM medical appointments should be available only when the patient is undergoing major surgery; the General Practitioner / Family Physician cannot perform the preoperative haematological assessment. Indeed, shifting to a wide-ranging PBM focus and its application to all surgical candidates has been widely linked with: improvements in costs; mitigation of patient risk; reduction of complications; and increased patient safety.[9,15,28-30] However, PBM has been commonly presented as both a patient-centred and a hospital-centred model,[28] and so it is worth reinforcing agreement on the potential inclusion of the General Practitioner / Family Physician in the preoperative haematological assessment.

Concerning the parameters and timings of preoperative and postoperative evaluations, the experts agreed that: both the preoperative and the postoperative evaluation should include the evaluation of reticulocytes; in patients with stable volaemia, the evaluation of CBC, ferritin, and transferrin saturation should be performed 12 to 24 hours after surgery; in the postoperative period the evaluation of CBC, ferritin, and transferrin saturation should be performed in all patients with anaemia (preoperative or postoperative), before hospital discharge. Conversely, they disagreed that postoperative clinical instability of patients in PBM programs does not change the timings to evaluate CBC, ferritin, and transferrin saturation. These findings are equally reflected by other studies, which: recognize the relevance of measuring the reticulocyte count before and after surgery[31-33]; refer to the re-evaluation of CBC, ferritin, and transferrin saturation in the first 24 hours following surgery (although the lowest haemoglobin levels mays be seen three to four days after surgery)[34]; and highlight the patient-focused approach, depending on its physiological and clinical statuses – arguing that patients should be followed after surgery to ensure continued management of their anaemia during their hospital admission and after discharge.[9] The panel's agreement is reinforced by the final topics, in which it is stated that ferritin levels can be modified after surgery, as well as that ferritin can be a valid marker for iron deficiency.

As for anaemia or iron deficiency treatment in the preoperative period, the specialists disagreed that in a patient with anaemia or iron deficiency which has only been documented the day before surgery there is no need to start preoperative treatment. They equally disagreed that it is mandatory to postpone elective surgeries of anaemic patients who have started anaemia correction in the preoperative period. Indeed, the published evidence supports the fact that preoperative anaemia is associated with a worse prognosis, and thus emphasizes the need for its correction before surgery.[35,36] Nonetheless, it has equally been argued that treatment of anaemia and iron deficiency should start as early as possible in the preoperative period [37] and that in particular circumstances it may be beneficial to postpone surgical procedures until anaemia improvement or resolution.[38] Regarding anaemia or iron deficiency treatment in the postoperative period, the specialists disagreed that: transfusion of red cell concentrates is the best strategy to treat anaemia in the immediate postoperative period (48 hours); the preferred treatment for anaemia in the postoperative period is transfusion of red cell concentrates. In fact, despite anaemia being known as an independent risk factor for morbidity and mortality in elective surgeries, blood transfusions have equally been independently associated with morbidity and mortality.[11,28] Finally, combined disagreement levels were above the established threshold when mentioned that iron deficiency without anaemia during the postoperative period should not be treated and that erythropoiesis stimulant agents have no place in the postoperative correction of anaemia. Iron deficiency is acknowledged as an independent entity beyond anaemia, worth treating on its own, regardless of anaemia being its leading symptom.[8,39] Furthermore, erythropoiesis stimulant agents are known to be potentially beneficial in the perioperative period, by improving survival rates, decreasing blood transfusions and shortening hospitalization.[26,40] As such, these agents are often recommended within preoperative decision algorithms, but their suitability in postoperative similar algorithms has also been mentioned.[10]

About the postoperative follow-up (Topic C), the respondents agreed that, at the postoperative 30-day revaluation, the surgeon should re-evaluate the CBC, ferritin, and transferrin saturation. This finding reinforces the relevance of including several medical specialities and their expertise within a patient-centred PBM approach. Also, on this topic, the experts disagreed that a stable patient with controlled anaemia at the date of hospital discharge will not require subsequent follow-up. Once again, this is in line with the current recommendations in terms of follow-up of anaemic patients, which may imply monitoring and interventions beyond the hospital stay.[32,34]

Limitations

Due to the nature of this study's methodology, as well as the need to comply with privacy and personal data regulations, it is not possible to differentiate the inputs from experts working in different medical domains, which may

introduce bias in the obtained results in terms of medical specialty representativity.

CONCLUSION

Prior studies have highlighted the consensual relevance of establishing an individualized plan, within the context of PBM as the standard of care, and of valuing preoperative and postoperative PBM interventions, thus highlighting the relevance of correcting anaemia and ID in the perioperative context.

In this Delphi panel, experts established as consensual that PBM medical appointments should exist for all patients who are candidates for elective surgeries in which blood products are expected to be used and that after surgery it is equally important to correct anaemia and iron deficiency. However, our results point out that convergent perspectives from a broad range of medical specialties exist**,** as do knowledge gaps in PBM principles and thus future training and literacy initiatives could be useful. These, focusing on harmonised practices in minimising or avoiding blood transfusion, would allow to further help the development and implementation of PBM standards in Portuguese hospitals, reducing morbimortality in post-surgery patients, costs and increasing availability of hospital beds.

AUTHORS CONTRIBUTION

ARN, DB: Planning and design of the work; data analysis; writing and critical review of the manuscript.

AM: Concept of the work; panel management; data analysis; writing and critical review of the manuscript.

VB, DG, JGA, FL, JM, TML: Member of the focus group; critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The material submitted conforms with regulations currently in force regarding research ethics. The work was performed in accordance with the principles of the Declaration of Helsinki updated in 2013.

DATA CONFIDENTIALY

The authors declare having followed the protocls in use at their working center reagarding patients' data publication.

COMPETING INTERESTS

TML: Received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Incyte, Jansen and Novartis.

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Anemia da Doença Renal Crónica: O Estado da Arte

Anemia in Chronic Kidney Disease: The State of the Art

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RESUMO

O envelhecimento populacional tem-se traduzido no aumento de prevalência de doenças crónicas como a doença renal crónica. A anemia é uma das complicações mais frequentes da doença renal crónica, com impacto não só na qualidade de vida como no prognóstico do doente e nos custos associados. O conhecimento nesta área terapêutica tem aumentado de forma significativa: desde o aparecimento da eritropoietina recombinante em 1989, passando pelo uso de doses crescentes de ferro parentérico e, mais recentemente, a novas moléculas como os inibidores do *hypoxia-inducible factor*. Os autores pretendem rever, de uma forma pragmática, o estado da arte da anemia associada à doença renal crónica, desde a epidemiologia, à fisiopatologia, ao diagnóstico e ao tratamento.
Palavras-chave: Anemia/diagnóstico; Anemia/tratamento farmacológico; Anemia Ferropénica; Doença Renal Crónica/complicações; Inibidores de Prolil-Hidrolase/uso terapêutico

ABSTRACT

The aging of the population has led to an increased prevalence of chronic diseases such as chronic kidney disease. Anemia is one of the most frequent complications of chronic kidney disease, with an impact not only on the quality of life but also on the patient's prognosis and associated costs. Knowledge in this therapeutic area has increased significantly: from the appearance of recombinant erythropoietin in 1989, through the use of increasing doses of parenteral iron and, more recently, to new molecules such as *hypoxia-inducible factor* inhibitors. The aim of this article is to present a pragmatic review of the state of the art in the epidemiology, pathophysiology, diagnosis and treatment of anemia associated with chronic kidney disease.
Keywords: Anemia/diagnosis; Anemia/drug therapy; Anemia, Iron-Deficiency; Prolyl-Hydroxylase Inhibitors/therapeutic use; Renal Insufficiency, Chronic/complications

INTRODUÇÃO

Em 1827, Bright mencionou pela primeira vez a relação entre a presença de anemia e a doença renal,[1] mas o papel do rim na produção de eritropoietina (EPO)[2] demorou mais de um século a ser descrito. Em 1985 surgiram as primeiras publicações sobre a clonagem do gene da eritropoietina[3,4] e apenas quatro anos depois é aprovada pela Food and Drug Administration (FDA) e pela European Medicines Agency (EMA) a primeira eritropoietina recombinante (rEPO) para tratamento da anemia associada à doença renal crónica (DRC). Ainda que esta molécula tenha criado a expetativa de uma cura definitiva da anemia da DRC, estudos posteriores vieram mostrar que a esperança que se depositou foi defraudada por um aumento do número de eventos adversos. Este artigo pretende rever, de forma prática, a fisiopatologia da anemia associada à doença renal crónica, o diagnóstico diferencial, as atuais abordagens terapêuticas e perspetivas futuras.

Definição de anemia da doença renal crónica

Define-se anemia como a diminuição de eritrócitos no sangue. Esta redução pode ser avaliada pela medição direta dos eritrócitos ou pela redução da concentração de hemoglobina ou hematócrito (estes últimos mais frequentemente utilizados). A Organização Mundial da Saúde (OMS) definiu anemia no homem e na mulher como valores de hemoglobina (Hb) inferiores a 13 e inferiores a 12 g/dL, respetivamente.[5] Os mesmos valores são utilizados pelas recomendações da *Kidney Disease Improving Global Outcomes* (KDIGO), as normas de orientação clínica mais utilizadas na Nefrologia em todo o mundo, para definir anemia associada à DRC.[6] A anemia da DRC deve-se, sobretudo, à diminuição da produção de eritrócitos e à diminuição da sobrevida dos mesmos, sendo habitualmente normocítica e normocrómica. Outras causas podem contribuir para a sua presença ou agravamento, como a deficiência de ferro - também muito habitual na DRC - e, neste caso, pode haver microcitose associada. Estas características serão fundamentais no estudo e diagnóstico diferencial da anemia em doentes renais.

Fisiopatologia da anemia da doença renal crónica

A eritropoiese ocorre na medula óssea em resposta à presença de EPO. Esta é sintetizada sobretudo nas células intersticiais peritubulares dos rins, e em pequena quantidade no fígado. O estímulo para a sua produção é a hipóxia. A diminuição da oxigenação sanguínea induz inibição

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da hidroxilação da subunidade alfa do fator de transcrição genética *hypoxia inducible factor* (HIF) que assim entra no núcleo celular, promovendo a transcrição de vários genes entre os quais os da EPO.[7] Na DRC, o número de células renais produtoras de EPO está diminuído, o que resulta na produção inadequada de EPO em resposta a estímulos hipóxicos e dá origem ao desenvolvimento de anemia. Os valores de eritropoietina estão muitas vezes dentro da faixa considerada normal, mas inferiores ao expectável para o grau de anemia. No que diz respeito à semivida dos eritrócitos, esta também está diminuída pelo ambiente urémico e inflamatório associado à DRC. O aumento de citocinas pro-inflamatórias, muito comum em doenças crónicas como a DRC, estimula a produção de hepcidina no fígado. A hepcidina é o principal regulador do metabolismo do ferro, atuando através do bloqueio da absorção de ferro no intestino e promovendo o seu sequestro nos macrófagos, diminuindo assim a sua disponibilidade para a síntese do heme (Fig. 1).[8]

Epidemiologia e impacto da anemia da doença renal crónica

A anemia é uma complicação muito frequente na presença de DRC, com grande impacto na sobrevida e qualidade de vida do doente. O problema é mais frequente quanto mais grave é o estádio da DRC (Fig. 2), sendo que no estádio 5 afeta até 95% dos doentes.[9]

A presença de anemia associa-se à duplicação do risco de morte por todas as causas[10] e ao aumento de eventos cardiovasculares, em comparação com doentes renais crónicos sem anemia.[11] Está ainda associada a maior progressão da DRC até ao estádio terminal.[12] O mecanismo pelo qual isto ocorre não está completamente estabelecido, não se podendo inferir se a anemia contribui como fator independente para a lesão renal ou se é apenas um marcador de gravidade da doença renal existente.

Além de conferir pior prognóstico, a anemia associa-se a também a perda de qualidade de vida.[13]

Em termos sociais e económicos, a presença de anemia associa-se ainda ao aumento dos custos globais com a doença renal, decorrentes dos tratamentos e das hospitalizações, que são muito mais frequentes nos doentes com anemia.[14]

Diagnóstico e diagnóstico diferencial

As manifestações clínicas da anemia da DRC são inespecíficas e em tudo sobreponíveis às de outras causas de anemia: fadiga, fraqueza, toracalgia, alterações do padrão do sono, taquicardia ou dispneia.

O diagnóstico passa pela confirmação laboratorial do valor diminuído de hemoglobina com volume globular médio e concentração globular de hemoglobina mantidas (anemia normocitica normocrómica). A abordagem diagnóstica é semelhante ao estudo de qualquer quadro de anemia (Fig. 3) porque o diagnóstico de anemia da doença renal crónica acaba por ser um diagnóstico que implica

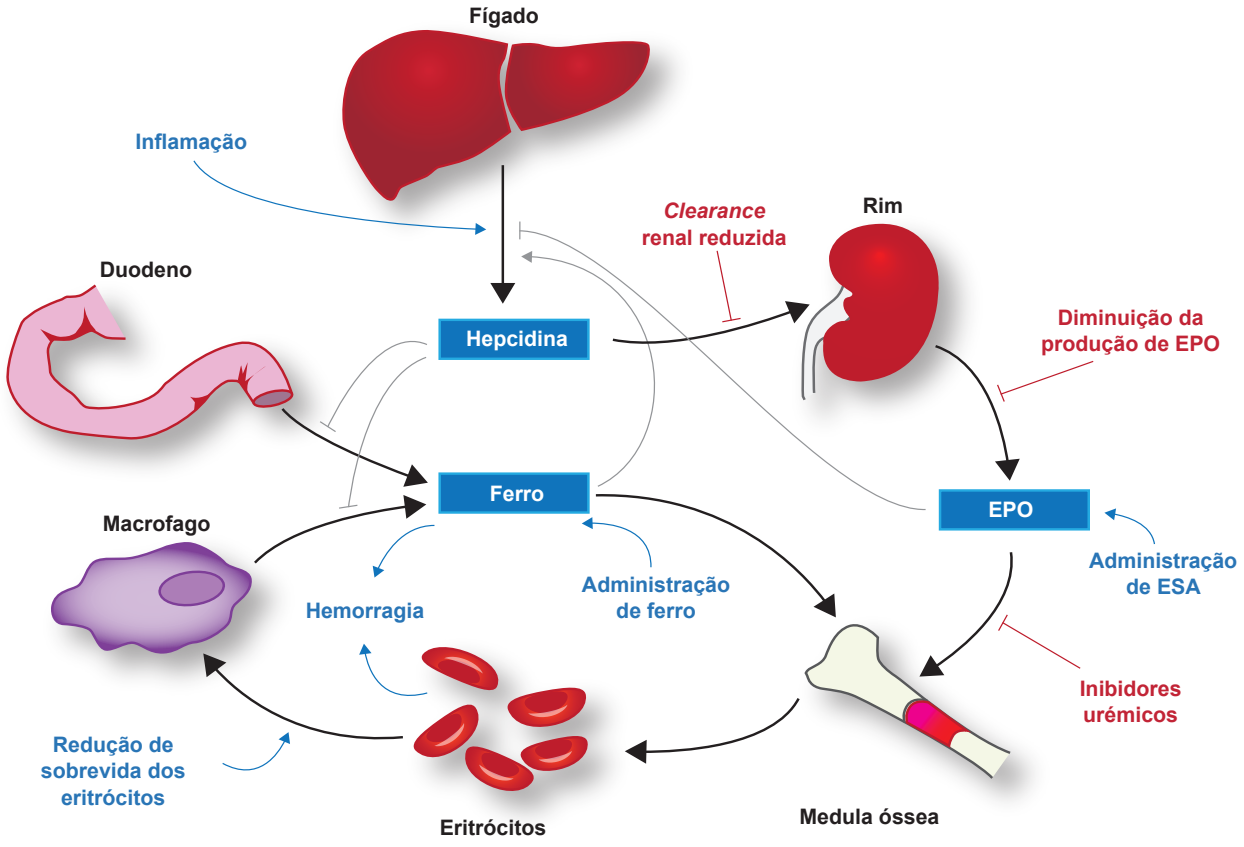

Figura 1 – Fisiopatologia da anemia da DRC
EPO: eritropoietina endógena, ESA: estimulador da eritropoiese

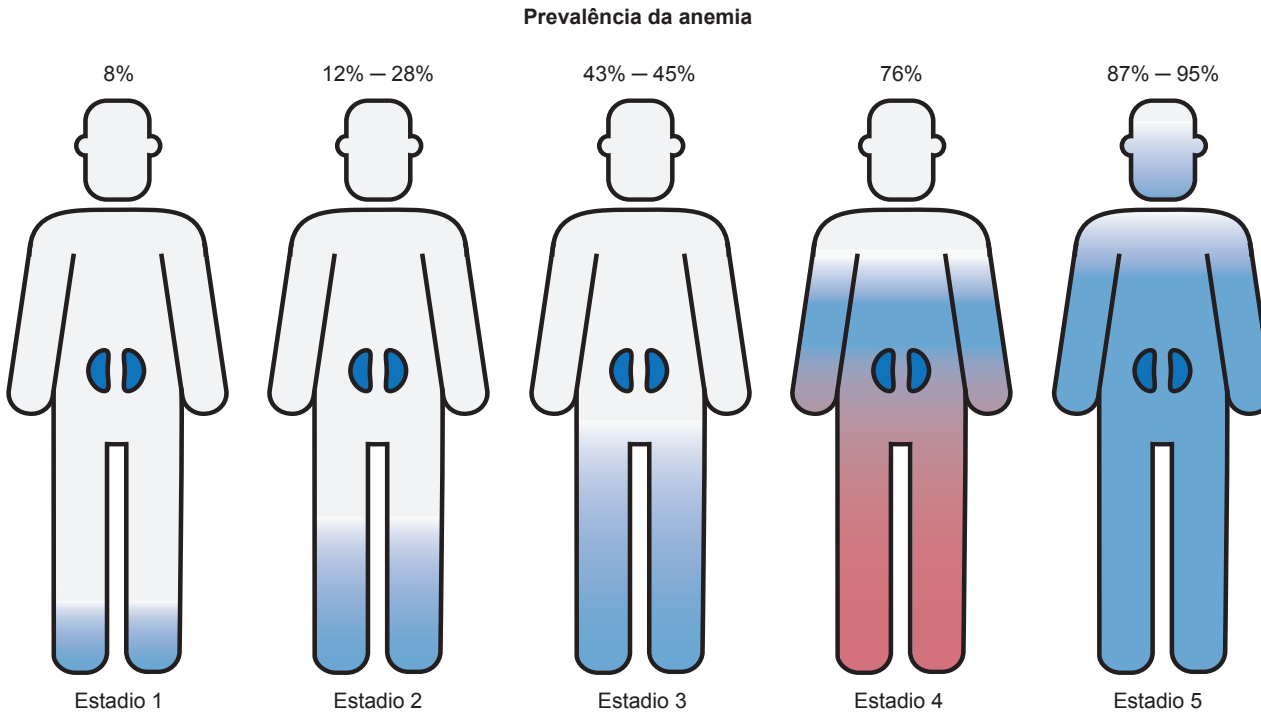

Figura 2 – Prevalência da anemia por estadio da DRC

exclusão de outras causas.[15] O doseamento dos valores de EPO é dispensável, uma vez que, conforme descrito na fisiopatologia, estes encontram-se frequentemente dentro dos limites da normalidade. A ferropénia é uma causa frequente de agravamento de qualquer anemia, e, portanto, a avaliação dos parâmetros do metabolismo do ferro e a sua correção são fundamentais. No diagnóstico de anemia associada à DRC, é relevante atender à desproporção entre a disfunção renal ligeira (estádios iniciais) e gravidade da anemia, o que deve levar a equacionar outras causas que devem ser excluídas (perdas de sangue, défices de hematínicos, patologia da medula óssea).[15]

Estado da arte no tratamento da anemia da doença renal crónica

O tratamento da anemia associada à DRC tem evoluído ao longo do último meio século. Desde a terapêutica de suporte com transfusões sanguíneas, passando pelos androgénios, a tecnologia avançou no sentido de encontrar soluções cada vez mais próximas da fisiologia humana.

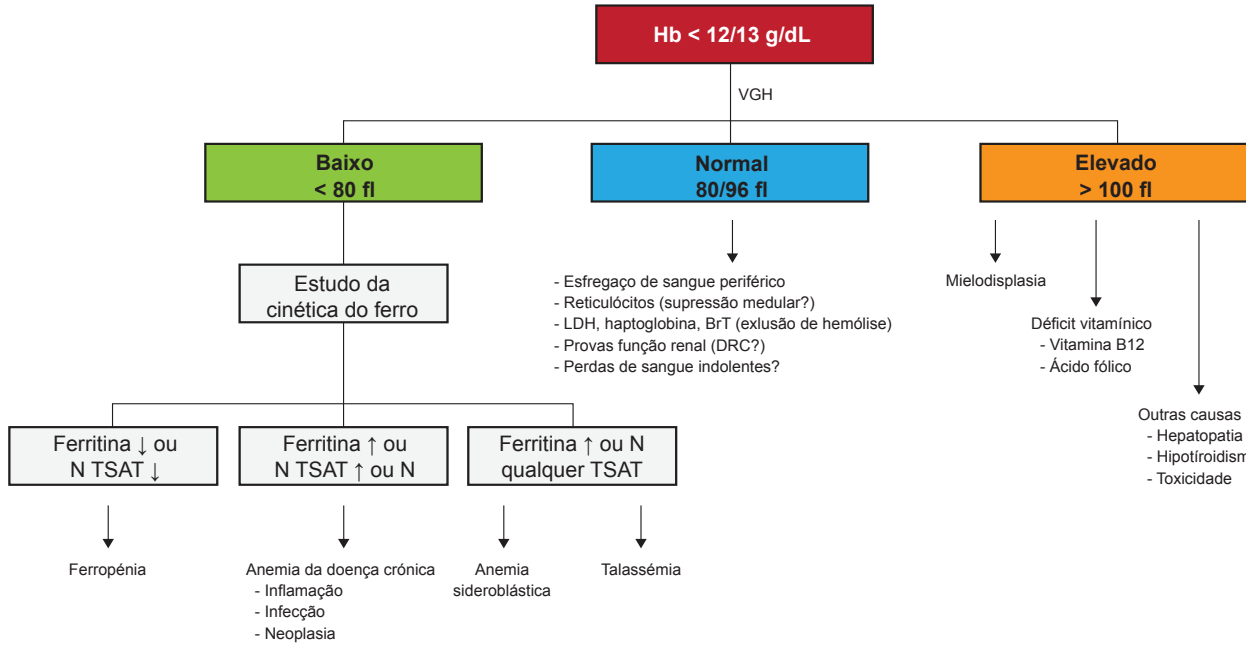

Figura 3 – Diagnóstico diferencial da anemia da DRC

Assim, surgiu a eritropoietina recombinante e mais recentemente os inibidores das HIF. A ferropénia, cuja importância terá sido inicialmente descurada, também tem sido alvo do tratamento nos nossos dias.

EPO recombinante

Até 1989, o tratamento da anemia na DRC consistia na administração periódica de transfusões de concentrado eritrocitário e terapêutica com androgénios. A descoberta e clonagem da rEPO criou a ilusão de que se conseguiria substituir o fator 'em falta' para uma eritropoiese eficaz e deste modo se curaria a anemia da DRC. A primeira molécula aprovada pela FDA e pela EMA foi a epoetina α e, um ano mais tarde, a epoetina β. A via de administração é parentérica - via intravenosa (IV) ou subcutânea (SC) - com necessidade de administração duas a três vezes por semana, sendo a semivida mais prolongada na via SC. Ainda assim, o incómodo desta prescrição levou ao desenvolvimento de rEPO com semividas mais longas: as de segunda geração - darbepoietina α - exigindo apenas administração semanal ou quinzenal e as de terceira geração - metoxi-polietenolglicol epoitina β [Continuous erythropoiesis receptor activator (CERA)] - com administração mensal, estas últimas sem diferença de semivida em relação à via parentérica de administração. Surgiram ainda no mercado moléculas biossimilares como a epoetina ζ a epoetina e a epoetina α biossimilar.

O facto é que a fisiopatologia desta situação clínica é complexa e os estudos que avaliaram o efeito da eritropoietina recombinante vieram reforçá-lo. Após a aprovação e introdução da rEPO no mercado, Besarab *et al*[16] publicaram o primeiro estudo aleatorizado que avaliava os efeitos da correção da anemia da DRC em doentes em diálise com insuficiência cardíaca ou cardiopatia isquémica. O estudo foi precocemente suspenso pelo aumento de eventos cardiovasculares (aumento da mortalidade e enfarte agudo do miocárdio) e de trombose do acesso vascular, nos doentes do braço de normalização da hemoglobina. Em 2006 foram publicados mais dois estudos aleatorizados que apontavam o mesmo cenário em doentes em pré-diálise: o estudo CHOIR (também precocemente suspenso pelo aumento de eventos cardiovasculares)[17] e o estudo CREATE.[18] Corrigir a hemoglobina com epoietina para valores acima de 11 g/dL associava-se a aumento de eventos cardiovasculares. Estes resultados foram definitivamente re-confirmados em 2009 quando foi publicado o estudo TREAT,[19] que avaliava os efeitos da correção da anemia em doentes diabéticos em pré-diálise com uma rEPO de segunda geração (darbepoietina alfa). Numa avaliação de mais de 4000 doentes aleatorizados para receber darbepoietina alfa com o intuito de atingir um valor de hemoglobina alvo de 13 g/dL ou uso de placebo, ambos os grupos apresentaram riscos semelhantes para os eventos compostos primários: morte/evento cardiovascular (enfarte agudo do miocárdio não fatal, insuficiência cardíaca, acidente vascular cerebral e hospitalização por isquemia miocárdica) ou morte/doença renal terminal. No entanto, houve um risco aumentado de acidente vascular cerebral fatal ou não fatal.

Não foi possível estabelecer uma explicação convincente para este aumento dos eventos cardiovasculares, embora várias hipóteses tenham sido levantadas[20]:

• A rapidez da subida da Hb, que levaria à hemoconcentração e aumento da viscosidade sanguínea e lesão endotelial;

• Um eventual efeito tóxico direto da rEPO sobre o endotélio.

Outros efeitos adversos devem ser ponderados na prescrição de rEPO. No estudo TREAT objetivou-se um aumento das mortes por causas neoplásicas - um efeito biologicamente plausível, uma vez que as células cancerígenas possuem recetores da EPO - que levou à introdução de uma advertência no seu uso em doentes com neoplasia ativa.[21]

Outra situação observada em utilizadores de epoetina α foi a aplasia eritróide pura, causada por anticorpos circulantes que neutralizam tanto rEPO como a eritropoietina nativa, induzindo uma anemia severa, apenas controlável através de transfusões sanguíneas.[22]

Em 2012, as normas da KDIGO apresentavam recomendações para apenas serem prescritas rEPO após uma abordagem individualizada, de acordo com a taxa de descida de Hb, o risco da necessidade de transfusões e a resposta à terapêutica com ferro, nos seguintes cenários:

• Em DRC em pré-diálise, para valores de Hb inferiores a 10 g/dL.

• Em DRC em diálise para valores de Hb inferiores 9 g/dL.

Enfatizou também a importância de não serem utilizadas rEPO para manter valores de Hb superiores a 11,5 g/dL e contraindicou firmemente a sua utilização para valores acima de 13 g/dL.

Para garantir estes alvos, é fundamental avaliar o doente sob rEPO até um mês após a sua introdução (subida previsível de Hb de 1 a 2 g/dL por mês) e ajustar a dose em conformidade. Se não se observar uma resposta adequada, as normas de orientação clínica da KDIGO sugerem um teto terapêutico até ao dobro da dose adequada ao peso ou dose habitual nos doentes previamente estáveis (Tabela 1).[6]

Tabela 1 – Dose inicial das diferentes rEPO por via parentérica

rEPO	Dose/peso	Frequência de administração
Epoetina	20 a 50 UI/kg (~2000 UI)	três vezes/semana
Darbepoetina	0,45 µg/kg (~20 a 30 µg) a 0,75 µg/kg	semanal - quinzenal
CERA	0,6 µg/kg (~30 a 60 µg) a 1,2 µg/kg	quinzenal - mensal

A era do ferro

A desilusão com o uso de rEPO focou as atenções em outros fatores fundamentais para a síntese de hemoglobina, entre os quais o ferro. As normas de orientação clínica da KDIGO definiram ferropénia com alvos em contexto inflamatório, ou seja, para valores de ferritina inferiores a 500 pg/dL e/ou taxa de saturação de transferrina inferior a 30% tanto para doentes em diálise como em pré-diálise.[6] Surgiram estudos a comparar formulações orais e parentéricas, doses crescentes de ferro IV.[23] Tornou-se evidente que a suplementação com ferro, sobretudo por via IV, contornando o aumento da hepcidina inerente à condição inflamatória da DRC, permitia usar menores doses de rEPO.[24] Em 2016 houve mesmo a necessidade de esclarecer melhor as recomendações acerca da utilização de ferro, à luz da nova evidência científica nesta área.[25]

Alguns dos riscos classicamente associados ao uso de doses crescentes de ferro, como a estimulação do crescimento bacteriano, o aumento do risco de infeção e toxicidade celular direta, o aumento do risco de progressão de doença aterosclerótica, de insulinorresistência por toxicidade das células ß pancreáticas ou de hemocromatose secundária[26] foram sendo apaziguados por estudos como o PIVOTAL.[27]

Assim, na prática clínica, um défice absoluto ou funcional de ferro deve ser corrigido. A escolha de uma formulação oral ou IV dependerá de várias condições (doente em pré-diálise/diálise peritoneal ou hemodiálise; valor de Hb, custos e recursos, etc.). É importante reconhecer que o ferro desempenha um papel essencial no metabolismo energético global do organismo pelo que, mesmo na ausência de anemia, deve ser corrigido.[28]

Falência terapêutica

Apesar da utilização de doses crescentes de ferro e de rEPO, existem muitas situações em que a resposta à terapêutica não é a esperada. As causas são múltiplas e devem ser investigadas, pois a sua correção poderá resolver a falência terapêutica (Tabela 2).

Tabela 2 – Causas de não resposta à terapêutica

Causas relacionadas com o doente
Idade
Raça
Genética
Hipotiroidismo
Comorbilidades
Diabetes *mellitus* ou insulinoresistência
Hospitalização recente
Causas relacionadas com a doença renal crónica
Perdas no circuito de hemodiálise
Síndrome inflamação-malnutrição
Doença mineral óssea
Diálise sub-ótima
Tempo em diálise
Função renal residual
Alumínio
Causas relacionadas com medicação
Não adesão à terapêutica
Bloqueio do sistema renina angiotensina aldosterona (IECAs)
Citotóxicos
Imunossupressores
Aplasia eritróide pura mediada por anticorpo
Causas hematológicas
Ferropénia
Perdas de sangue
Hemólise
Hemoglobinopatia
Déficit de vitamina B12 ou ácido fólico
Déficit de carnitina
Síndromes mielodisplásicos

Novos tratamentos na anemia da DRC

Apesar da exclusão das causas acima referidas de ausência de resposta (ou resposta inadequada) às terapêuticas atuais, existem situações em que se mantém a anemia não controlada. Este fenómeno traduz-se no aumento da mortalidade destes doentes e no aumento dos custos do tratamento. Assim, a pesquisa de novas moléculas levou à descoberta de agentes estabilizadores do HIF. Estes fármacos atuam inibindo a hidroxilação da subunidade α da HIF que transloca assim para o núcleo, induzindo a transcrição da EPO (Fig. 4).[29] O aumento da EPO induzida pelo HIF leva à diminuição da produção de hepcidina, libertando ferro para uma eritropoiese eficaz.[30] Por outro lado, os inibidores da HIF parecem ter também um efeito direto na absorção de ferro no intestino,[31] aumentando assim a sua biodisponibilidade por dois mecanismos distintos. O aumento da eritropoiese endógena e promoção da biodisponibilidade de ferro, contornando os efeitos da inflamação, constituem a maior esperança deste novo grupo de fármacos. Existem ainda outras vantagens, tais como a administração por via oral, potencialmente benéfica não só em fase pré-dialítica ou em programa de diálise peritoneal, mas também pela maior facilidade de armazenamento e distribuição já que não requer refrigeração. No entanto, a maior expetativa diz respeito ao impacto na mortalidade cardiovascular. Apesar dos estudos preliminares não mostrarem variação no perfil tensional e se associarem a uma melhoria do perfil lipídico, não houve diferenças estatisticamente significativas nos eventos cardiovasculares.[33] Além disso, desconhecem-se ainda efeitos a longo prazo como o efeito na progressão da DRC, na promoção da carcinogénese (ou outras patologias dependentes da angiogénese, como a retinopatia diabética) e o efeito no tónus vascular.[33]

Apesar de já estarem comercializadas em alguns países como o Japão,[32] estas moléculas aguardam ainda aprovação pela FDA e pela EMA.

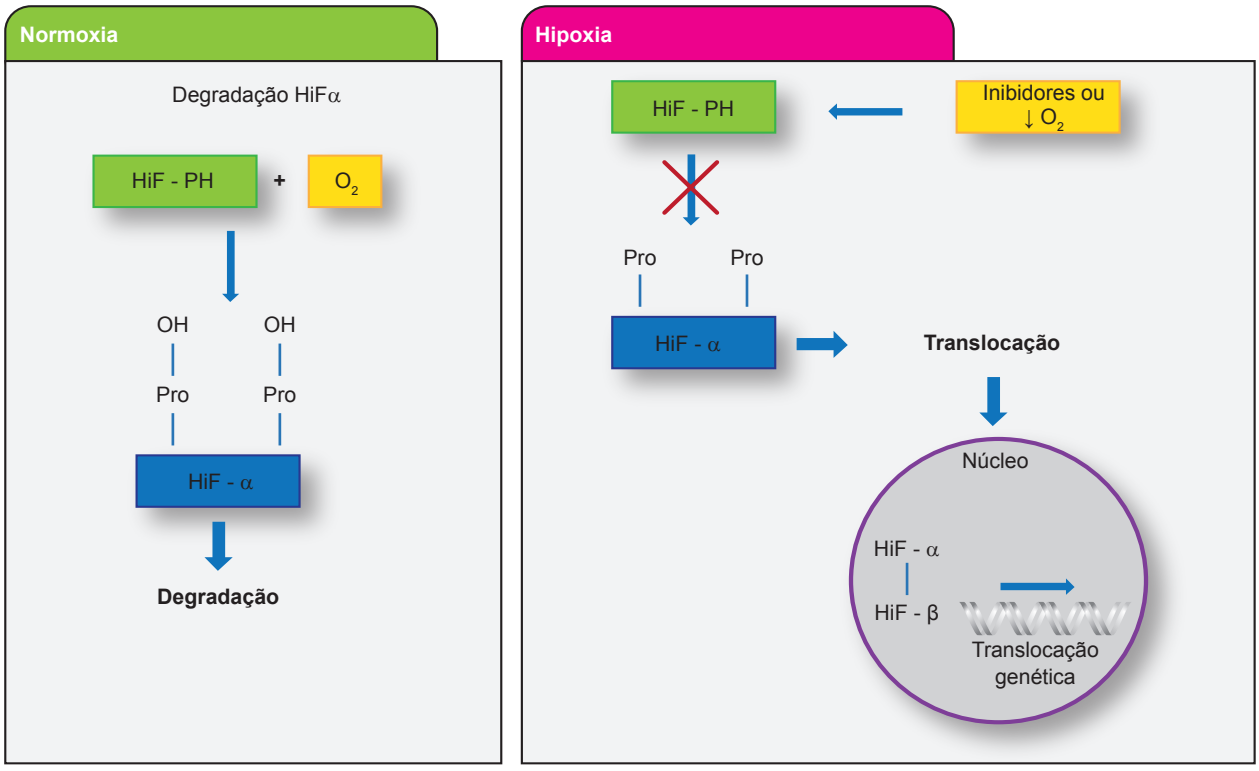

Figura 4 – Mecanismo de acção dos inibidores das HIF

CONCLUSÃO

O aumento da prevalência de DRC traduzir-se-á inevitavelmente num aumento da prevalência de anemia. Fazer o diagnóstico diferencial da causa da anemia é fundamental para tratar adequadamente o doente. O maior reconhecimento da fisiopatologia da anemia da DRC tem permitido o desenvolvimento de novas soluções terapêuticas. É muito relevante que todos os médicos que acompanham doentes renais, conheçam as indicações e recomendações de cada opção, uma vez que nenhum fármaco é isento de riscos. O estado da arte do tratamento desta condição tão comum deve começar pela correção da ferropénia, definida à luz da doença renal crónica e só depois se devem iniciar rEPO. O papel de novos fármacos como os inibidores das HIF ainda estão por definir, mas poderão vir a responder a algumas lacunas do tratamento atual, entre as quais a posologia de administração, o *bypass* ao mecanismo inibitório da inflamação crónica ou à associação entre a correção da anemia e o aumento dos eventos cardiovasculares trombóticos.

CONTRIBUTO DOS AUTORES

AF: Conceção do artigo.

ARN, JM, CF: Revisão do artigo.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Inflammatory Myofibroblastic Tumour of the Common Bile Duct

Tumor Inflamatório Miofibroblástico da Via Biliar Principal

CASO CLÍNICO

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ABSTRACT

Inflammatory myofibroblastic tumour is a rare entity of indeterminate biological potential with a reduced tendency for recurrence and metastasis. Although it can arise from multiple organs, the bile duct is a very rare site of origin. We report the case of a 75-year-old asymptomatic male with elevated gamma-glutamyl transferase [1575 U/L (12 - 64 U/L)] and alkaline phosphatase [271 U/L (40 - 150 U/L)]. Computed tomography showed a 17 mm hypervascular lesion in the confluence of the right and left hepatic ducts, with bile duct ectasia and right liver lobe atrophy. The patient was initially managed as having a Klatskin tumour and underwent right hepatectomy. Histology showed a spindle cell proliferation with an inflammatory infiltrate of lymphocytes, plasma cells and collagen-rich stroma, consistent with an inflammatory myofibroblastic tumour. He was discharged 30 days after admission, and nine months later remains asymptomatic. His liver function tests have normalized and follow-up tests are unremarkable.

Keywords: Bile Duct Neoplasms; Hepatic Duct, Common; Hepatectomy; Klatskin Tumour; Liver Function Tests

RESUMO

O tumor miofibroblástico inflamatório é uma entidade rara com comportamento biológico indeterminado e reduzido potencial de recorrência e metastização. Apesar de poder surgir em vários órgãos, as vias biliares constituem uma localização incomum. Descreve-se o caso de um homem de 75 anos, assintomático, com elevação da gama glutamil transferase [1575 U/L (12 - 64 U/L)] e fosfatase alcalina [271 U/L (40 - 150 U/L)], que realizou uma tomografia computorizada evidenciando uma lesão hipervascular com 17 mm na confluência dos ductos biliares, com ectasia das vias biliares intra-hepáticas à direita, e atrofia do lobo hepático correspondente. O caso foi abordado inicialmente como um tumor de Klatskin e realizada hepatectomia direita. A histologia relevou uma proliferação de células fusiformes com infiltrado inflamatório de linfócitos, plasmócitos e estroma rico em colágeno, compatível com tumor miofibroblástico inflamatório. Após nove meses, o doente permanece assintomático, com testes de função hepática com valores normais e sem sinais imagiológicos de recidiva.

Palavras-chave: Ducto Hepático Comum; Hepatectomia; Neoplasias dos Ductos biliares; Testes de Função Hepática; Tumor de Klatskin

INTRODUCTION

Inflammatory myofibroblastic tumours (IMT) were previously considered under the group of inflammatory pseudotumours, but now comprise a separate entity of fibroblastic/myofibroblastic neoplasms with prominent inflammatory infiltrates and intermediate biological potential.[1,2] These tumours are commonly seen in the lungs of children and young adults, but seemingly rare in other locations.[1]

We describe the case of an asymptomatic patient who presented with long-term elevation of gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP), with no bilirubin elevation, caused by a hypervascular common bile duct lesion. The lesion was surgically removed and later shown to be an IMT.

CASE REPORT

We report the case of a 75-year-old male with incidental findings of altered hepatic function tests, particularly, raised gamma glutamyl transferase and alkaline phosphatase, associated with progressive bile duct ectasia. Bilirubin levels were normal and there were no signs or symptoms of disease.

An abdominal computed tomography (CT) detected an intraluminal hypervascular lesion located in the confluence of the right and left bile ducts. The lesion measured 17 mm, showed prominent bile duct ectasia, particularly of the right hepatic ducts, and right lobe atrophy, along with thrombosis of the posterior branch of the right portal vein (Figs. 1, 2 and 3).

Blood tests showed gamma glutamyl transferase (GGT) levels of 1575 U/L (12 - 64 U/L) and alkaline phosphatase (ALP) levels of 271 U/L (40 - 150 U/L), with only slightly elevated alanine aminotransferase (ALT) of 98 U/L (0 - 55 U/L) and normal bilirubin levels of 0.90 mg/dL. The tumour markers CA 19.9, CEA and alpha-fetoprotein were negative.

The patient remained asymptomatic until he was admitted for a right liver hepatectomy for suspected hilar cholangiocarcinoma, which was completed with no immediate complications. After one day in the intensive care unit, he was transferred to the surgical ward. Eleven days later,

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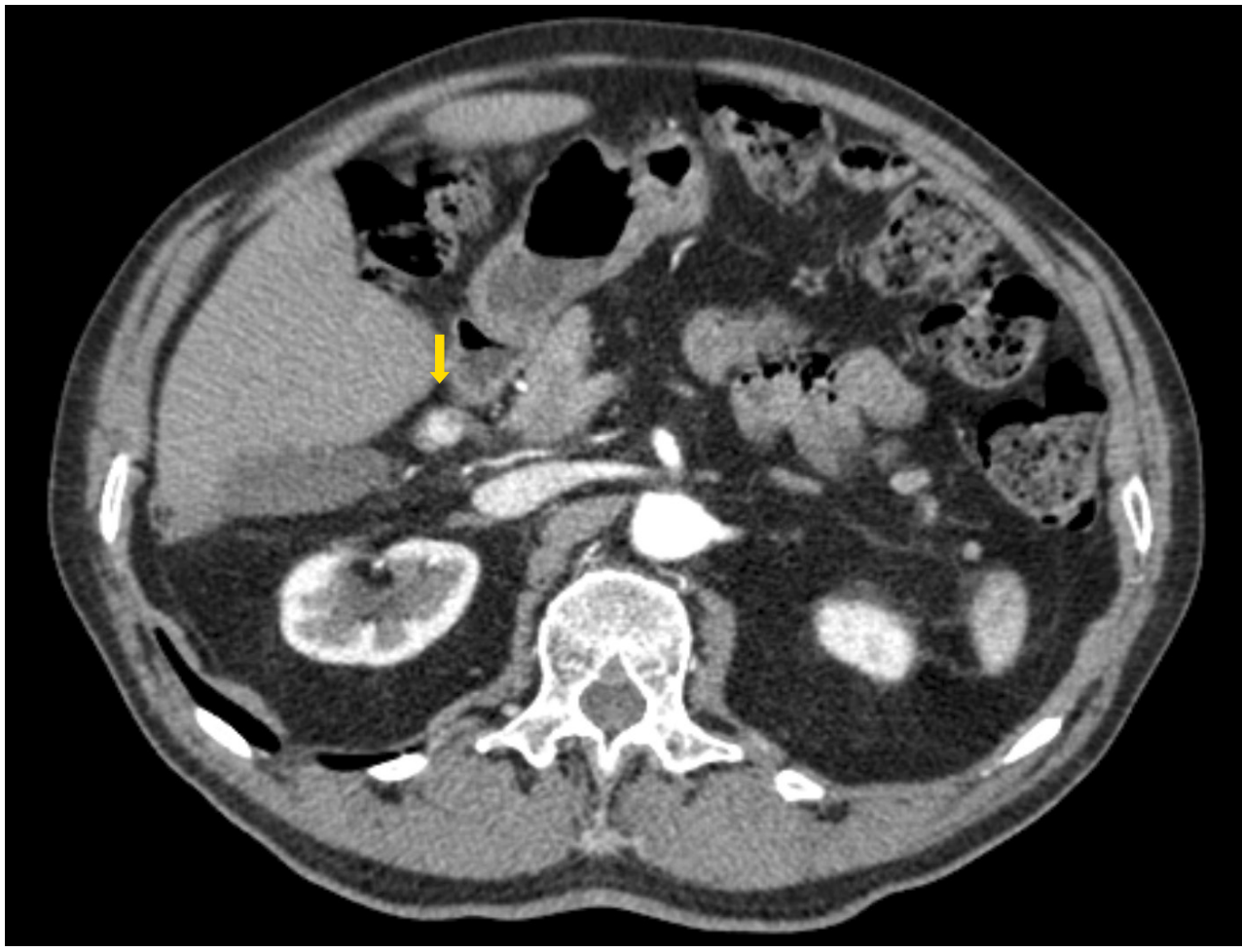

Figure 1 – Arterial phase CT showing a hypervascular lesion on the proximal common hepatic duct

there was a slight leukocyte elevation (from 9.1 x 10^9/L to 11.35 x 10^9/L), and therefore, a CT scan was performed. The scan showed a pneumoperitoneum and a collection along the line of the hepatectomy, consistent with a biloma. The patient underwent a second surgery to drain the collection and wash the abdomen. In addition, a biliary leak along the course of the hepatectomy was detected and promptly repaired. Although suspected, no dehiscence of the bilioenteric anastomosis was seen. The patient recovered well and was discharged 15 days after the second surgery, 30 days after admission.

Histologically, the lesion partially occluded the lumen of the bile duct and consisted of a mesenchymal tumour of epithelioid and spindle cells with vesicular nuclei, with a fascicular architecture immersed in a collagenous stroma, admixed with plasma cells and lymphocytes (Figs. 4 and 5). Mitotic activity was low, and no necrosis was present. The tumour cells did not express ACTIN, DESMIN, ALK or ROS 1. Although the immunohistochemistry pattern was not characteristic, the tissue samples were reviewed in a cancer centre and the tumour diagnosed as an inflammatory myofibroblastic tumour (IMT).

Nine months after admission, hepatic function tests normalized, follow-up tests were unremarkable and there was no bile duct ectasia.

DISCUSSION

Inflammatory myofibroblastic tumours are rare tumours of indeterminate biological potential, that can involve any anatomical location, with the lungs being the most affected site. The colon and small intestine are the most frequently involved gastrointestinal sites, but involvement of the biliary ducts is very uncommon with only a few reported cases. The etiopathogenesis of IMT in the bile ducts is not clear in the literature, with various reported theories, including prior infections or an autoimmune nature.[3-5]

IMTs predominantly affect children and young adults but have been described in any age.[1,6] Site-specific symptoms have been described such as abdominal pain or gastrointestinal symptoms for intrabdominal lesions. Hepatic IMTs may present with abdominal pain, fever, biliary obstruction and/or portal hypertension due to obliterative phlebitis. An inflammatory syndrome consisting of fever, weight loss and malaise is seen in 15% - 30% of patients.[1,4,5]

The reported imaging findings of IMT in the literature appear to be inconsistent and non-specific, probably due to its low incidence and its heterogeneous histopathologic features. As such, distinction from malignant neoplasms is often not possible. In general, hepatic lesions are well-circumscribed with variable enhancement patterns, usually heterogenous or peripheral in the arterial phase.[4-7]

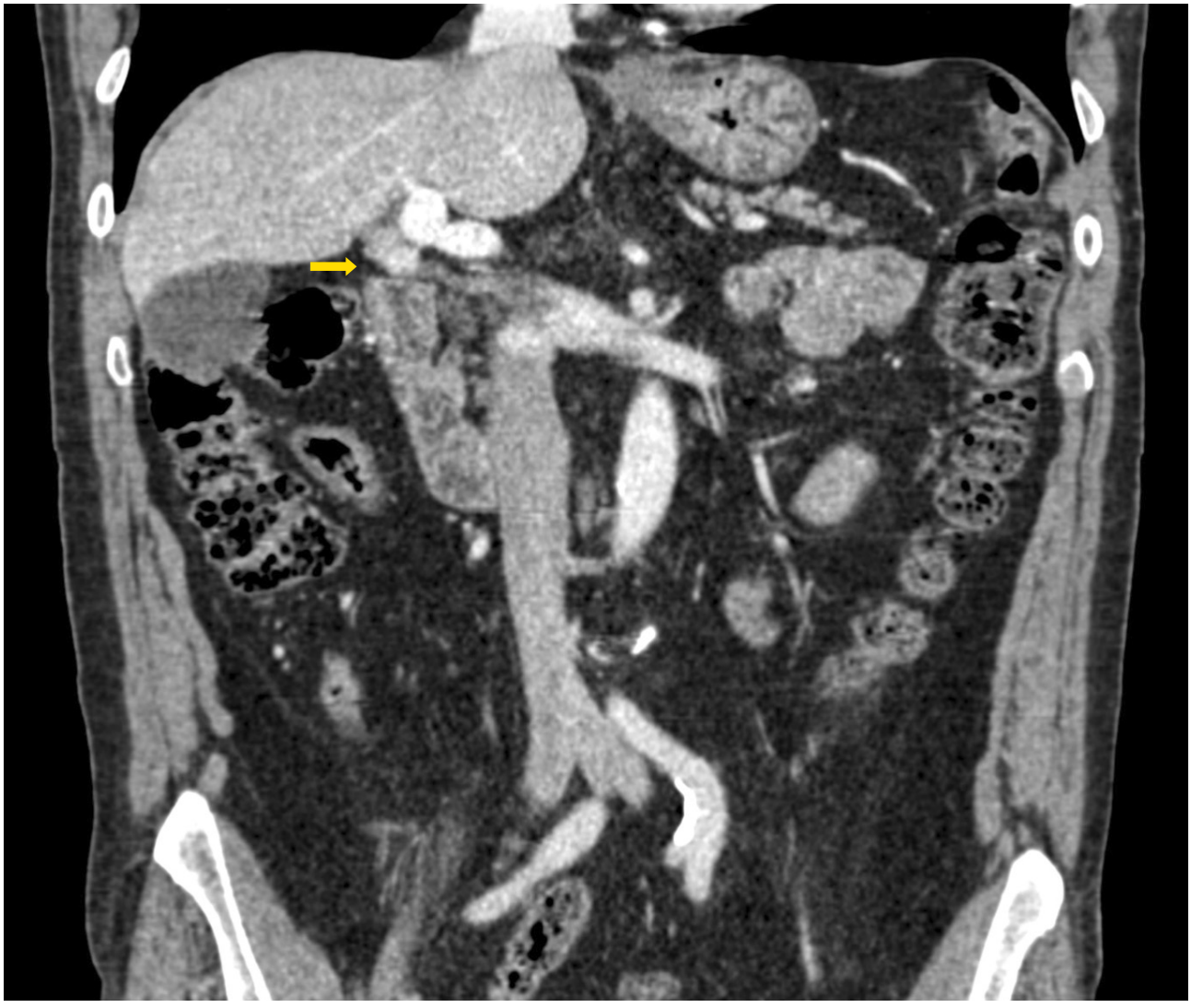

Figure 2 – Portal-venous phase coronal CT reconstruction showing persistent enhancement of the tumour on the proximal common hepatic duct, at the point of confluence of the left and right hepatic ducts

Brush cytology obtained by endoscopic retrograde cholangiopancreatography (ERCP) is frequently inconclusive, and therefore diagnosis is usually histological. Direct cholangioscopy with biopsy is an option. However, even if it shows signs of IMT, concerns regarding the adequacy of the samples are often raised. Therefore, a definitive diagnosis is usually based on analysis of postoperative material.[8] Histological examinations usually reveal fascicles of cytologically bland spindle cells. The stroma may be myxoid or collagenous, usually containing an inflammatory infiltrate dominated by lymphocytes and plasma cells. Tumours can exhibit a compact fascicular architecture with minimal stroma or be sparsely cellular with a sclerotic stroma. Mitotic activity is low, and necrosis is usually absent. IMTs are positive for smooth muscle actin (SMA) in nearly all cases and can also express desmin and keratin. Nearly 60% of IMTs express ALK and 5% express ROS1.[1,2,9] However, immunohistochemistry is not essential to confirm the diagnosis, due to the variable expression of myofibroblastic markers. ALK positivity is helpful if present, but its absence does not exclude de diagnosis of IMT, especially in adults.[1]

The clinical course of IMTs is unpredictable. These tumours typically show a benign clinical behaviour, with slow growing, rarely metastasizing (< 5%) lesions, although recurrence rates for extrapulmonary IMT can be as high as 25%.[1,2,4]

Complete surgical removal is the mainstay of treatment, although anti-inflammatory drugs and chemoradiotherapy have been used in some cases.[5,6] In advanced or unresectable IMTs with ALK immunoreactivity, specific tyrosine kinase inhibitors such as crizotinib can be considered as the standard of care.[3,4] Regular long-term follow-up is required because of the tumour's recurring and metastasizing nature.

Due to the absence of specific symptoms or imaging features and extremely rare incidence, a diagnosis of IMT prior to surgery is challenging. In the present case, it was initially misdiagnosed as a Klatskin tumour due to its much higher occurrence and frequent perihilar location. However, there was a long history of altered hepatic functions tests,

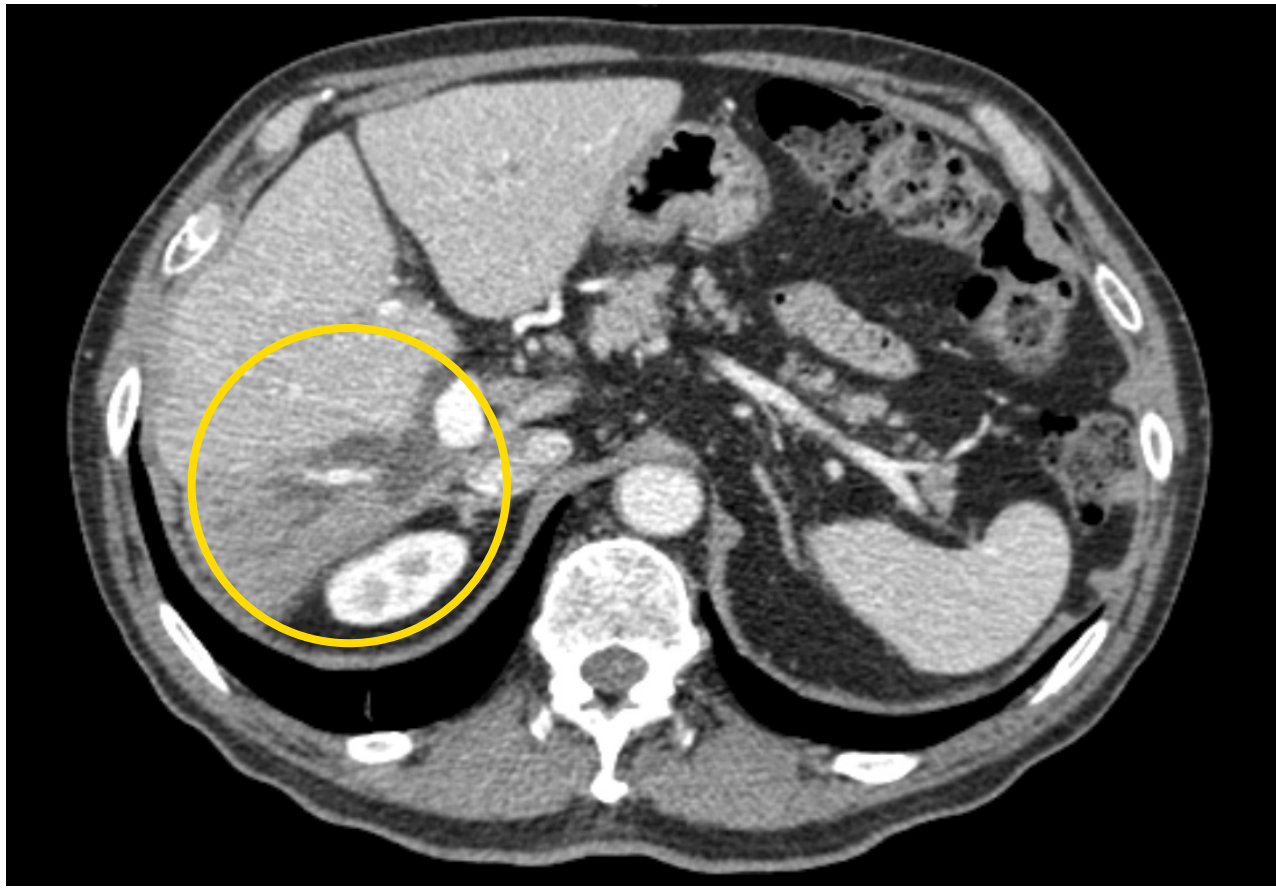

Figure 3 – Enhanced CT showing atrophy of the right hepatic lobe with compensatory hypertrophy of the left lobe, secondary to biliary obstruction by tumour

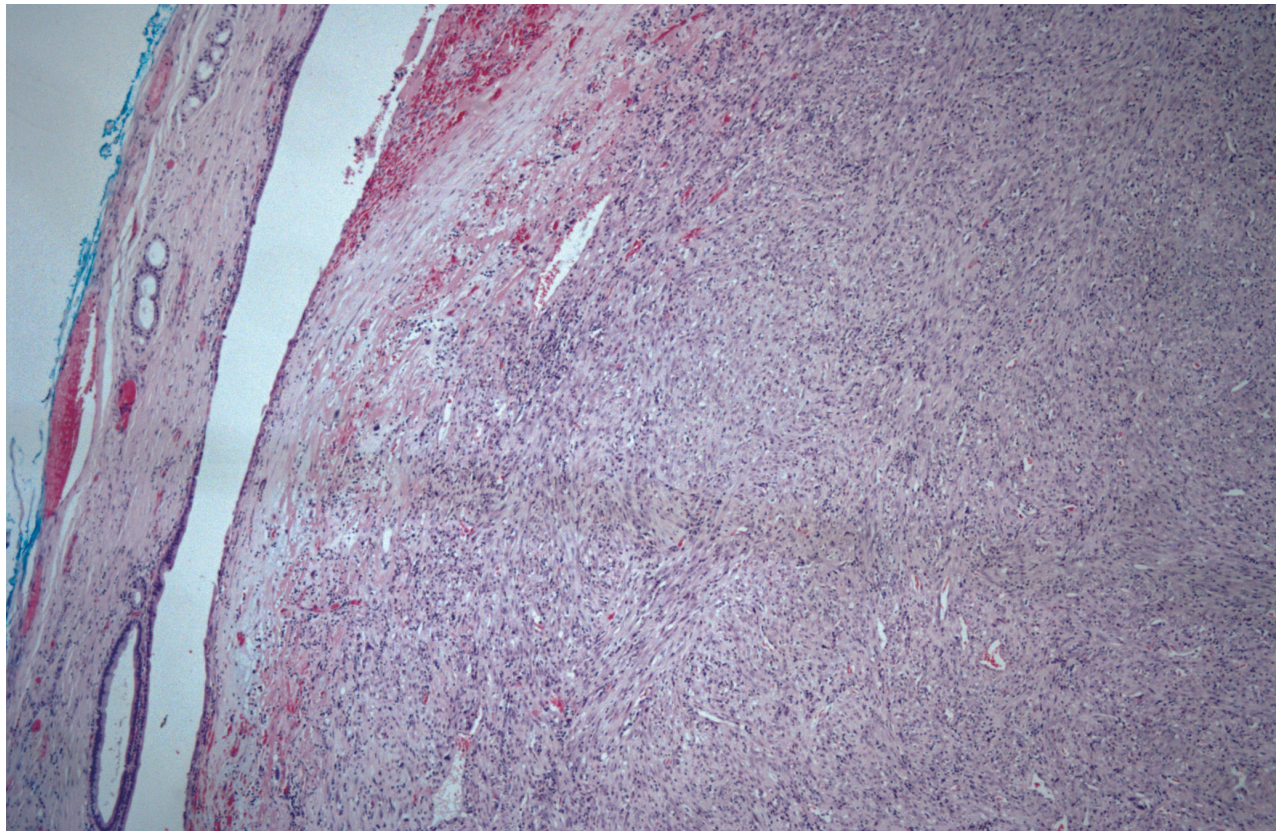

Figure 4 – Low power view of microscopic sample demonstrating a biliary duct occluded by a cellular spindle cell proliferation (HE - 40x)

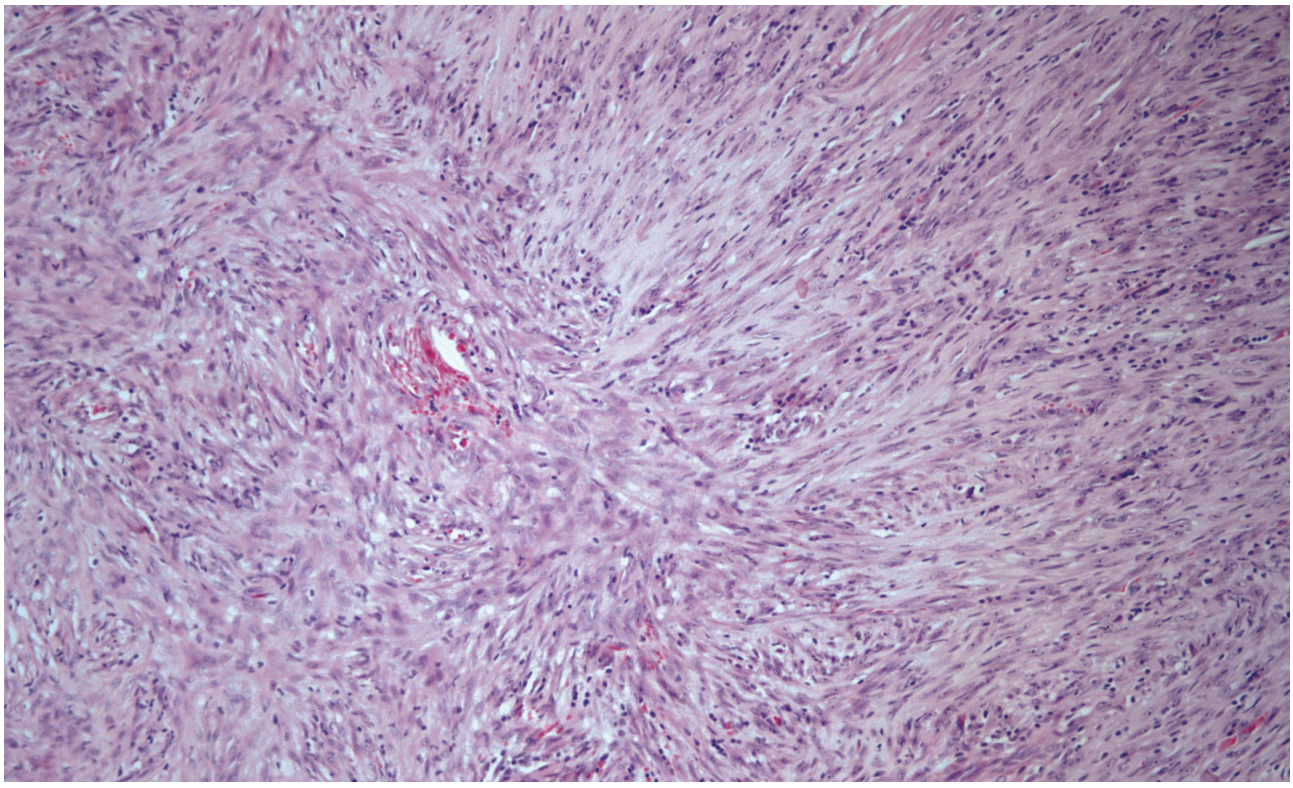

Figure 5 – Microscopic sample showing fascicles of spindle cells admixed with an inflammatory infiltrate (HE -100x)

which did not support an aggressive process, and the imaging features of hypervascularity and intraductal nature of the lesion were atypical of extrahepatic cholangiocarcinoma. These discrepant features, when present, may not be enough to establish the diagnosis of an IMT, but should raise suspicion of a diagnosis other than cholangiocarcinoma.

AUTHORS CONTRIBUTION

MAS: Research, draft of the paper.
AC, TB: Draft and critical review of the paper.
RM: Critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

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The First Documented Case of Hb South Florida Variant in Portugal

O Primeiro Caso da Variante Hb South Florida em Portugal

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ABSTRACT

We present a 39-year-old male, previous smoker, with no other known cardiovascular risk factors. He was referred to Internal Medicine for study of thrombophilia, because of repeated deep vein thrombosis. Multiple diagnostic tests were undertaken where HbA1c assay was included. The result was 14.6%. The patient did not have a prior diagnosis of diabetes and denied any symptoms. Fasting blood glucose and blood count did not reveal any changes. A further analysis of hemoglobin subtypes showed the presence of an unclassified variant. The sample was sent to a Portuguese reference center and, through molecular biology, an *HBB* mutation in heterozygosity was identified, coding for an hemoglobin variant - Hb South Florida (c.4G > A; p.Val2Met), which was for the first time documented in Portugal. We emphasize the importance of considering the presence of hemoglobin variants when HbA1C values are discrepant from the clinical presentation.

Keywords: Diabetes Mellitus; Glycated Hemoglobin A; Hemoglobins, Abnormal

RESUMO

Apresenta-se o caso de um homem de 39 anos, ex-fumador, sem outros fatores de risco conhecidos. Foi encaminhado à consulta de Medicina Interna para estudo de trombofilia por tromboses venosas profundas de repetição. Foi realizado estudo etiológico, onde o doseamento da HbA1c foi incluído. O resultado foi de 14,6%. O doente não apresentava diagnóstico prévio de diabetes *mellitus* e negava sintomas compatíveis. A glicemia em jejum e o hemograma não revelaram alterações. O estudo por eletroforese das hemoglobinas revelou uma variante não classificada. Num centro de referência português foi identificada, por biologia molecular, uma mutação em heterozigotia no gene *HBB* associada a uma variante de hemoglobina - Hb South Florida (c.4G > A; p.Val2Met), sendo a primeira vez que é documentada em Portugal. Salienta-se a importância de, na presença de valores de HbA1C discrepantes da apresentação clínica, considerar a presença de variantes de hemoglobina.

Palavras-chave: Diabetes Mellitus; Hemoglobina A Glicada; Hemoglobinas Anormais

INTRODUCTION

South Florida hemoglobin (Hb) is a rare variant of Hb that causes, depending on the methodology used, an erroneous elevation of glycosylated hemoglobin (HbA1c). Since its first description in 1986,[1] six cases have been reported in the world literature. This article shows a review of the seventh case in the world, and the first in Portugal.

CASE REPORT

A 39-year-old male with repeated deep vein thrombosis was referred to an internal medicine clinic for the investigation of possible thrombophilia. He had a great left saphenous vein thrombosis, a few years ago, for which a surgery was performed. Six months later he had a new event, with thrombosis of the left popliteal vein. In this context, treatment with rivaroxaban was started.

He had obesity, treated with bariatric surgery over 10 years ago and since then, had a normal weight; he also had a history of prior smoking habits. No other cardiovascular risk factors were known, as well as any related family conditions.

Diagnostic tests were requested including the HbA1c assay. The result was 14.6% (provided by the ion-exchange high performance liquid chromatography – HPLC), although the patient had no previous symptoms suggestive of diabetes such as hyperglycemia, weight loss, polydipsia, polyuria or tiredness (normal range of HbA1C is 3.4% - 5.8% by HPLC). He denied taking medicines other than rivaroxaban. He had no known condition that increased the life of red blood cells, such as anemia due to iron deficiency, asplenia or high levels of urea. He reported no recent episodes of bleeding or blood transfusions. Fasting blood glucose and a simple blood count were normal. His creatinine level was 1.0 mg/dL, and no uremia was noted. The remaining blood tests showed: an Hb of 13.9 g/dL, a hematocrit of 41.4 %, a slight microcytosis (MCV 78.9 fL, normal range 80 - 96 fL) with hypochromia (MCH 26.5 pg, normal range 28 - 34 pg); bilirubin and lactate dehydrogenase levels were normal.

A detailed study of hemoglobin subtypes by Hb electrophoresis was performed. The patient' results revealed: Hb A2 = 2.5%, F = 0.1%, A1c = 3.4%, and the presence of a variant not classified by the methodology (93%). The blood sample was sent to a Portuguese reference center for the study of hemoglobinopathies and it was possible, through molecular biology and DNA screening, to identify that the patient was heterozygous with a beta chain Hb variant. He was found to have the South Florida variant (c.4G > A; p.Val2Met), which for the first time was described in Portugal. His family members have not been screened for

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this type of mutation.

As for the thrombophilia study, only a heterozygous mutation for the *MTHFR* gene (mutation C677T) was detected. He had no recurrence of thrombotic episodes while maintaining anticoagulant therapy.

DISCUSSION

Hb South Florida is a recently identified clinically silent hemoglobin variant that migrates with hemoglobin A, on ion exchange chromatography.[3] In the Hb South Florida, the Hb structure seems to function normally. This variant is characterized by the replacement of a neutral amino acid for a charged one, with valine substituted by methionine.[2] The only evidence for the presence of Hb South Florida was the finding of amounts of glycosylated hemoglobin in non-diabetic samples.[3] Normally, the healthy adult hemoglobin consists of approximately 97% HbA, 2.5% HbA2 and 0.5% HbF,[2] with other variants not specified if having no pathological significance. Aberrant HbA1c readings secondary to Hb variants seem to be an uncommon occurrence, and the exact incidence is unknown.[4]

Therefore, the frequency of this hemoglobin variant is unknown and rare. More than 1500 individual families have been evaluated and do not have hemoglobin South Florida.[3] There are only six cases reported in the literature, and, to our knowledge, no case has been reported in Portugal until now.

Certain conditions are known to misleadingly lower HbA1C, such as: bleeding, hemolytic disease, haemoglobinopathies and myelodysplastic disease; while others can give falsely high HbA1C levels such as: chronic anemia, renal failure and uremia (that can have high concentrations of carbamylated hemoglobin, resulting in aberrantly high HbA1C).[5]

Due to the high importance of HbA1c monitoring, more than 300 analytical methods have been developed for its analysis, such as immunoassay, high pressure liquid chromatography, spectrophotometry, ion-exchange and affinity chromatography, electrophoresis, boronate affinity chromatography, colorimetric methods, and mass spectroscopy. Ion-exchange chromatography is the method commonly used to measure the total rapidly migrating fraction of hemoglobin A, but only the molecular biology method is able to identify this hemoglobin variant.

Hb South Florida has been described six times in the literature, but there are other clinically silent Hb variants that can present with falsely elevated HbA1C values. Some are Hb Santa Juana (Beta 108 Asn → Ser), also known as Hb Serres, that has been widely reported in Greek and Mexican populations; Hb Takamatsu (Beta 120 Lys → Gln); Hb G-Szuhu (Beta 80 Asn → Lys) and Hb Camperdown (Beta 104 Arg → Ser).[6, 7]

However, these variants do not correlate with any symptoms or clinical disorder; as such, our patient's thrombotic events could not be attributed to this genetic finding.

The HbA1c test remains an essential tool in monitoring glucose control in patients with diabetes mellitus, and it has been widely recommended as a diagnostic test for diabetes.

It is important for clinicians to interpret the results of HbA1C on a clinical context and be aware of discrepancies. When there are inconsistencies between a patient's blood glucose monitoring and laboratory measured HbA1c, a falsely elevated or lowered HbA1c result should be suspected. It is also important to know that there are many other Hb variants in the population, some of which are clinically silent but can interfere with routine laboratory tests. Such subtle changes in the amino acid sequence, may explain, in part, the great variation of human response to the same environmental agents.[3]

These aspects should lead to further investigation for abnormal Hb variants, in order to prevent the misdiagnosis and inadvertent treatment of diabetes.

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AUTHORS CONTRIBUTION

MBM: Concept and design of the paper, draft of the manuscript, approval of the final version

LD, VG: Concept and design of the paper, draft of the manuscript.

CR: Critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

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Groove Sign: A Clue to the Diagnosis

Sinal do Sulco: Uma Pista para o Diagnóstico

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Keywords: Eosinophilia; Fasciitis; Fibrosis; Skin
Palavras-chave: Eosinofilia; Fasceíte; Fibrose; Pele

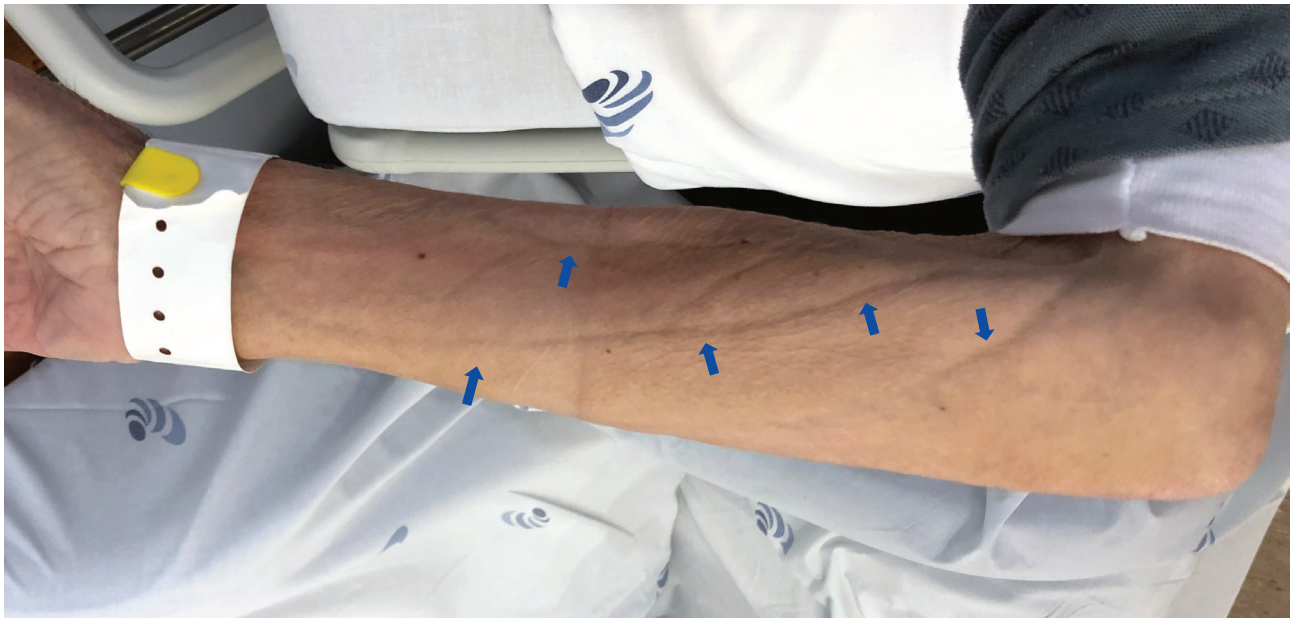

Figure 1 – Groove sign: indentation of the skin along the course of the forearm veins (arrows)

A 75-year-old man presented with a 4-month history of edema, erythema and progressive skin thickening affecting the limbs. No triggers were identified. His past medical history was irrelevant. The physical examination revealed induration in the upper and lower limbs, sparing the hands, feet, face and trunk. Linear depressions along the course of the veins, exacerbated by limb elevation, were present on the forearms, and were consistent with the groove sign (Fig. 1). The laboratory findings included peripheral eosinophilia (1800 cells/μL) and elevated C-reactive protein and aldolase (respectively 31.1 mg/L, normal value < 3.5; 19.6 U/L, normal value < 7.6). The antinuclear antibodies were negative. The magnetic resonance imaging showed a soft tissue edema with a fascial predominance. The fascial biopsy was compatible with eosinophilic fasciitis (EF). The patient started oral prednisolone 0.5 mg/kg/day and subsequently oral methotrexate 20 mg/week with cutaneous and functional improvement over 1-year follow-up.

EF is a rare fibrosing disorder of unknown etiology which is often misdiagnosed.[1,2] The groove sign reflects fibrosis and tethering of connective tissue around the veins, and it is a classical feature of EF.[3]

AUTHORS CONTRIBUTION

MSR, MB: Medical follow-up of the patient; draft of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

INFORMED CONSENT

Obtained.

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COMPETING INTERESTS

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Impact of ADHD and OCD in Portuguese and Brazilian Patients with Tourette Syndrome During the COVID-19 Pandemic

Impacto da PHDA e POC em Indivíduos Portugueses e Brasileiros com Síndrome de Tourette durante a Pandemia de COVID-19

Keywords: Attention Deficit Disorder with Hyperactivity; COVID-19; Obsessive-Compulsive Disorder; Tourette Syndrome
Palavras-chave: COVID-19; Perturbação de Hiperatividade e Défice de Atenção; Perturbação Obsessivo-Compulsiva; Síndrome de Tourette

Starting in China, in 2020, COVID-19 spread all over the world, affecting the mental health of billions of people. Tourette syndrome (TS) is a neurodevelopmental disorder defined by multiple motor and at least one phonic tic.[1] Around half of the patients with tics reported an exacerbation during the COVID-19 pandemic.[2–4] Comorbidity with attention-deficit/hyperactivity disorder (ADHD) and/or obsessive-compulsive disorder (OCD) is as high as 90% in TS and exacerbates the clinical expression.[1] Contextual changes such as those imposed by the COVID-19 pandemic (e.g., fear, disruption of routines, and isolation) also affect tic severity. Studies show that both comorbidities and socioeconomic factors influenced the clinical course of tics during the pandemic.[2,3] In Portugal, a perceived increase in tics and related manifestations, including functional tics, raised the attention of social media (e.g., *Revista Sábado*, October 31st, 2021, and *Jornal Observador*, November 21st, 2021). The Portuguese TS Association reported an increasing call for help from families and individuals with TS, which created the need for further research.

Our study aimed to investigate the role of ADHD and OCD in tic severity during the COVID-19 pandemic, in Portuguese and Brazilian patients with TS (approved by the Ethics Committee of the Coimbra Hospital and University Center). Between July and December 2021, through the social media of the Portuguese and Brazilian TS Associations, we assessed 22 Portuguese-speaking individuals with TS (68% male, 32% female; age range between 16 and 54 years old) with the Portuguese versions of the Adult ADHD Self-Report Screening Scale–version 1.1 and the Obsessive-Compulsive Inventory–Revised. Participants graded their tic severity during the outbreak on a 5-point Likert scale. Descriptive, Spearman-correlation, and Mann-Whitney-U analyses were conducted using the software SPSS, version 26.

Approximately half of the participants (54.5%) reported that their tics were a little (31.8%) or much worse (22.7%) since the outbreak. Eight patients (36.3%) reported that their tics remained stable, and 9.1% perceived a slight improvement. Self-reported tic worsening correlated with more ADHD ($r = 0.602$, $p = 0.003$) and hoarding ($r = 0.425$, $p = 0.048$) symptoms. Accordingly, the group of patients with TS who reported tic worsening experienced more hoarding ($Z = -2.434$; $p = 0.015$) and ADHD ($Z = -2.376$; $p = 0.017$) symptoms. Between-group differences were non-significant for the other obsessive-compulsive dimensions (all $p > 0.38$).

While the lack of statistically significant differences in obsessive-compulsive symptoms may simply reflect a lack of statistical power, the selectivity of our findings might also mean that hoarding and ADHD symptoms reflect an underlying phenotype,[5] which was more susceptible to the effects of the pandemic. Need-based hoarding (e.g., masks, soaps) may increase in response to the COVID-19 threat as a way of increasing the perception of control.[6] Staying at home for prolonged periods may disrupt coping strategies (e.g., sports and physical activity) of individuals with ADHD symptoms.[7]

Despite several limitations (e.g., the subjective nature of self-report instruments, the cross-sectional design, and the small sample size of our study), our results overlap with those of previous studies showing that a significant proportion of patients with TS experienced a worsening in their tics during the COVID-19 pandemic.[3,4] Furthermore, our study indicates that patients with TS suffering from hoarding and ADHD symptoms may be particularly vulnerable and may need a more thorough follow-up.

ACKNOWLEDGMENTS

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AUTHORS CONTRIBUTION

AA: Conceptualization and design of the work, data acquisition, analysis and interpretation, conception of the first draft, critical review and editing of the manuscript.

FC: Data acquisition, analysis and interpretation, conception of the original draft, critical review and editing of the manuscript.

VAC, ATP: Data acquisition, analysis and interpretation, critical review and editing of the manuscript.

AM: Critical review and editing of the manuscript, supervision of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors have followed the protocols of their work center on the publication of data. The data was anonymized and none of the authors had access to patient identification. The study was conducted in accordance with the Helsinki Declaration updated in 2013.

DATA CONFIDENTIALITY

The authors declare that they followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

AA is a member of Associação Portuguesa de Síndrome de Tourette, unpaid.

VAC is the Vice President of Associação Portuguesa de Síndrome de Tourette, unpaid.

All other authors declared no conflicts of interest.

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Best Medical Treatment: What About the COMPASS Trial Strategy?

O Melhor Tratamento Médico: Onde Tem Lugar a Estratégia do Ensaio COMPASS?

Keywords: Aspirin/therapeutic use; Coronary Artery Disease/drug therapy; Platelet Aggregation Inhibitors/therapeutic use; Peripheral Arterial Disease/drug therapy; Rivaroxaban/therapeutic use
Palavras-chave: Aspirina/uso terapêutico; Doença Artéria Coronária//tratamento farmacológico; Doença Arterial Periférica/tratamento farmacológico; Inibidores da Agregação Plaquetária/uso terapêutico; Rivaroxabana/uso terapêutico

We read with interest the paper by Lopes *et al* reporting data about 'best medical treatment' (BMT) in patients admitted to a vascular surgery department. BMT was defined as treatment with antithrombotic and lipid-lowering treatment and, when appropriate, antihypertensive, and anti-diabetic drugs.[1] However, the anti-thrombotic drug chosen was not specified and the reasons for not being on BMT were not detailed. Unlike in clinical trials, real-world patients can present a significant number of uncontrollable variables that could influence both therapeutic decisions and outcomes.

We would like to call attention to a topic only briefly mentioned by the authors – the COMPASS trial strategy.[2]

In 2017, the COMPASS trial showed that using aspirin plus low-dose rivaroxaban in patients with stable atherosclerotic vascular disease reduced cardiovascular death, stroke, or myocardial infarction by 24%. Even when considering the bleeding risk, combination therapy had a net clinical benefit of 20%.[2]

Therefore, we considered it would be interesting to specify which antithrombotic strategy is chosen in these high-risk patients. In fact, most vascular surgery patients have peripheral artery disease (PAD) and hence meet inclusion criteria to start the COMPASS strategy. However, it is important to be aware of the broad exclusion criteria of this treatment (Table 1). We also hypothesize that therapeutic conservatism and physicians' resistance to change,[3] in addition to the last two years of the COVID-19 pandemic, may have reduced physicians' adherence to this new treatment strategy.[4]

To perceive how many patients met criteria to start the COMPASS strategy[2] we did an exploratory, observational, retrospective, and cross-sectional study. On a randomly selected day, the electronic records of all inpatients of the internal medicine department were screened. Inclusion and exclusion criteria of the COMPASS trial were applied. Ethics committee approval was waived due to the retrospective design and focus on data collected from electronic

Table 1 – Inclusion and exclusion criteria of COMPASS trial

Inclusion criteria	Exclusion criteria
Peripheral artery disease	
Previous bypass surgery or percutaneous angioplasty revascularization OR	High risk of bleeding
Previous amputation for arterial vascular disease OR	Stroke within 1 month or any history of hemorrhagic or lacunar stroke
History of intermittent claudication AND (≥ 1): - An ankle/arm BP ratio < 0.90, or peripheral artery stenosis (≥ 50%) OR	Severe heart failure with known ejection fraction < 30% or New York Heart Association (NYHA) class III or IV symptoms
- Previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50%	Glomerular filtration rate < 15 mL/min
	Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
Coronary artery disease	Non-cardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer)
≥ 65 years old; OR	History of hypersensitivity or known contraindication for rivaroxaban/aspirin
< 65 years old AND - atherosclerosis or revascularization involving at least 1 one additional vascular bed (e.g., the aorta, arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, kidneys); OR	Systemic treatment with strong inhibitors of both CYP3A4 and p-glycoprotein (e.g. ketoconazole, ritonavir), or strong inducers of CYP3A4 (e.g. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine)
- or at least 2 additional risk factors: - Current smoker; - Diabetes mellitus; - Glomerular filtration rate < 60 mL/min; - Heart failure; - Non-lacunar ischemic stroke ≥ 1 month ago.	Any known hepatic disease associated with coagulopathy Subjects who are pregnant or breastfeeding

BP: blood pressure

databases as part of patients' routine care.

Forty-eight patients (52% male) with a mean age of 74.8 ± 16.4 years-old were analyzed and 19% (n = 9) met criteria to start this strategy – of which 55% (n = 5) had coronary artery disease and 45% (n = 4) had PAD.

Nonetheless, only 4% (n = 2) were eligible when considering exclusion criteria. The most frequent exclusion criteria were the use of full dose oral anticoagulation due to atrial fibrillation, followed by poor medical prognosis. One of the patients was excluded due to being treated with clopidogrel, which could be switched to aspirin plus low-dose rivaroxaban to meet the COMPASS strategy, since it could have more clinical benefit.[2]

We consider that it is important to raise physicians' awareness to the inclusion and exclusion criteria of this new preventive strategy in order to potentially apply it in clinical practice.

AUTHORS CONTRIBUTION

SRJ, MA: Study design and conception. Data collection and analysis. Drafting, critical review and approval of the manuscript.

ARL: Data analysis. Drafting, critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors have followed the protocols of their work center on the publication of data. The data was anonymized and none of the authors had access to patient identification. The study was conducted in accordance with the Helsinki Declaration updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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Caracterização da Sobreinfeção na Infeção a SARS-CoV-2 num Serviço de Medicina Intensiva em Portugal

Bacterial Coinfection in Patients with SARS-CoV-2 in an Intensive Care Unit in Portugal

Palavras-chave: Coinfecção; COVID-19; Infecções Bacterianas; SARS-CoV-2; Unidades de Cuidados Intensivos
Keywords: Bacterial Infections; COVID-19; Coinfection; Intensive Care Units; SARS-CoV-2

Nos últimos anos, a infeção por SARS-CoV-2 foi uma causa frequente de admissão hospitalar, nomeadamente em Cuidados Intensivos, colocando novos desafios na nossa prática clínica.[1]

Sabe-se que, em pandemias prévias, a sobreinfeção representou uma das causas de maior mortalidade. Contudo, ainda pouco se sabe quanto a esta situação em indivíduos com infeção a SARS-CoV-2, e ainda menos em indivíduos com maior vulnerabilidade a intercorrências infeciosas, como os doentes com diabetes ou doentes sob corticoterapia crónica. Assim, foi realizado um estudo no Serviço de Medicina Intensiva (SMI) do Centro Hospitalar Médio Tejo em Abrantes, com o objetivo de caraterizar a sobreinfeção em doentes com infeção a SARS-CoV-2, a sua prevalência e possíveis fatores de risco associados.

Este estudo descritivo retrospetivo analisou doentes com SARS-CoV-2 admitidos no SMI entre março de 2020 e fevereiro de 2021 (n = 152). Os dados foram obtidos a partir de registos clínicos do Serviço. A análise estatística foi realizada através do *software* R, tendo sido usados os testes *t* e qui-quadrado de forma a avaliar a significância estatística, que foi definida para valores *p* inferiores a 0,05. Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados, garantindo a confidencialidade. Uma vez que se trata de um estudo retrospetivo descrevendo apenas dados clínicos agregados não foi necessária a aprovação ética para o mesmo.

Dos 152 doentes incluídos, 70 (46%) tinham diabetes *mellitus* tipo 2 e oito (5%) estavam sob corticoterapia crónica. A prevalência de sobreinfeção na população geral foi de 58% (n = 88), 61% (n = 43) no grupo com diabetes e a 50% (n = 4) no grupo sob corticoterapia.

A infeção respiratória foi a mais prevalente, contabilizando 83 (47%) casos, seguida da bacteriémia em 33 casos (19%) e infeção urinária em 55 (32%) dos casos. De entre os agentes causadores de sobreinfeção, as bactérias (n = 144, 84,2%), nomeadamente os bacilos gram negativos, foram os agentes mais frequentes. Por sua vez, a infeção fúngica esteve presente em apenas 27 casos (15,8%), responsáveis na sua maioria por quadros de infeção urinária. Não foram evidenciadas sobreinfeções víricas.

A sobreinfeção conferiu pior prognóstico aos doentes com COVID-19 grave (Tabela 1). De facto, estimou-se que a presença de sobreinfeção aumentou o tempo de internamento no SMI em quatro dias e o tempo sob ventilação mecânica em cinco dias; condicionou um aumento de quatro pontos no SOFA *score* médio e esteve associado a um risco 4,2 vezes superior de choque séptico, em comparação com doentes sem sobreinfeção (IC 95%: 3,09 – 6,67; $p < 0,01$) O risco de morte foi 2,2 vezes superior em doentes com pelo menos uma intercorrência infeciosa, em comparação com doentes sem sobreinfeção (IC 95%: 0,8 – 6,5; $p = 0,02$).

Quando analisamos o prognóstico e o foco infeccioso, verificou-se que a pneumonia associada ao ventilador

Tabela 1 – Características demográficas e relativas ao internamento

Características	Todos os doentes (n = 152)	Doentes sem DB (n = 82)	Doentes com DB (n = 70)	*p-value*	Doentes sem CC (n = 144)	Doentes sob CC (n = 8)	*p-value*
Idade, anos (DP)	64 (51 – 77)	60 (50 – 70)	65 (53 – 77)	–	64 (52 – 76)	64 (54 – 74)	–
Masculino, n (%)	103 (68%)	56 (68%)	47 (67%)	–	101 (70%)	2 (25%)	–
Tempo de internamento em UCI, média, dias (IC 95%)	7,94	6,91 (5,68 – 8,14)	8,83 (7,53 – 10,13)	**0,04**	6,63 (3,47 – 9,78)	8,02 (7,08 – 8,96)	0,35
Tempo de internamento hospitalar, média, dias (IC 95%)	17,67	15,76 (13,4 – 18,1)	17,87 (15,4 – 20,4)	**0,03**	17,67 (15,9 – 19,4)	15,77 (9,8 – 21,7)	0,85
Tempo sob ventilação mecânica invasiva, média, dias (IC 95%)	9,56	8,51 (6,19 – 10,8)	9,68 (7,64 – 11,7)	0,21	5,70 (0 – 11,92)	9,35 (7,79 – 10,92)	0,68
Sobreinfeção, n (%)	88 (58%)	37 (42%)	51 (73%)	0,06	82 (57%)	7 (83%)	0,15
Evolução para choque séptico, n (%)	37 (24%)	16 (20%)	21 (30%)	0,65	32 (22%)	5 (63%)	0,89
SOFA score inicial, média (DP)	5,57 (2,8 – 8,3)	5,57 (2,8 – 8,3)	5,43 (2,6 – 8,2)	–	5,57 (2,8 – 8,3)	5,29 (2,54 – 8,0)	–
Mortalidade, n (%)	49 (32%)	21 (25%)	28 (40%)	0,15	45 (34%)	4 (50%)	0,57

DB: diabetes *mellitus*; CC: corticoterapia crónica

(PAV) esteve associada a um aumento em 6,5 dias de internamento no SMI e a um aumento de sete dias de ventilação mecânica, quando comparado com quem não desenvolveu PAV. Da mesma forma, a PAV apresentou um risco 5,8 vezes superior de desenvolver choque séptico (IC 95%: 2,1 – 17,1; $p < 0,01$) e 2,8 vezes superior de morrer (IC 95%: 1,3 - 6,4; $p < 0,01$).

A bacteriemia esteve associada a um aumento em cinco pontos do SOFA *score* médio e a um risco 8,5 vezes superior de desenvolver choque séptico (IC 95%: 3,1 - 24; $p < 0,01$) e 3,3 vezes superior de morrer (IC 95%: 1,3 - 8,8; $p = 0,01$), quando comparados com doentes sem bacteriemia

Estes resultados são semelhantes aos encontrados em estudos europeus similares.[2]

Contrariamente ao que seria expectável, no nosso estudo não se observou uma maior predisposição para sobreinfeção nos doentes com diabetes ou sob corticoterapia crónica.[3,4] Contudo, os doentes com diabetes apresentaram uma média do tempo de internamento no SMI (8,83 dias) e hospitalar (17,87 dias) superior aos doentes sem diabetes (6,91 dias e 15,76 dias, respetivamente) sendo as diferenças estatisticamente significativas ($p = 0,04$ e $p = 0,03$, respetivamente).

À semelhança de outros estudos como o de Hugues *et al*,[5] a taxa de mortalidade foi de 32%.

A sobreinfeção agrava o curso clínico em doentes com COVID-19. Desta forma, a sua rápida suspeição é fundamental para melhorar o seu prognóstico.

CONTRIBUTO DOS AUTORES

ACD: Recolha de dados, análise estatística, redação do artigo.

SN: Redação e revisão do artigo.

TO: Recolha de dados.

TLP, AR, NC: Revisão do artigo.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial actualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

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Carta ao Editor em Relação à Diretriz "Protocolo Intra-Hospitalar para Abordagem da Doença COVID-19 no Adulto"

Letter to the Editor Regarding the Guideline "Intrahospital Protocol for the Management of COVID-19 Disease in Adults"

Palavras-chave: COVID-19/diagnóstico por imagem; Protocolos Clínicos; SARS-CoV-2; Tomografia Computorizada
Keywords: Clinical Protocols; COVID-19/diagnostic imaging; SARS-CoV-2; Tomography, X-Ray Computed

Foi com agrado que lemos o artigo de Barreiro *et al*,[1] uma norma em geral bem elaborada, atual e dirigida para o meio hospitalar.

Da nossa experiência e prática local, julgamos também adequada uma abordagem porventura um pouco mais criteriosa na requisição da tomografia computorizada (TC) mesmo no doente com doença grave à admissão. Uma boa radiografia de tórax, relatada e integrada com scores como o de Brixia ou o *Dutch* COVID-19 *risk model*, fornece muitas vezes elementos diagnósticos e prognósticos suficientes na admissão, ou mesmo no decorrer do internamento.[2]

Muitos doentes relativamente jovens e sem suspeição clínica de patologia pulmonar prévia relevante fizeram o seu trajeto nos nossos cuidados intensivos com um bom desfecho e recuperação, sem necessidade de TC.

O conhecimento da fisiopatologia da COVID-19 foi evoluindo gradualmente, e cedo se começou a descortinar, no meio radiológico, a hipótese de a pneumonia organizativa secundária ao SARS-CoV-2 não estar a ser devidamente considerada.[3] Sendo as características radiológicas tão similares ou mesmo indistinguíveis entre estas duas entidades, postula-se atualmente a sua interconexão na esperada evolução natural da doença.[4] De facto, a organização, caracterizada pela proliferação de fibroblastos, é uma resposta comum e praticamente universal à lesão pulmonar, seja ela focal ou difusa.[5] No processo organizativo, apesar da vasta gama de agentes etiológicos possíveis, a resposta do pulmão à lesão é bastante limitada, com um padrão reativo semelhante do ponto de visto radiológico e histológico, independentemente da causa subjacente.[5]

Relativamente ao embolismo pulmonar (EP), concordamos com a estratégia de que em caso de alto grau de suspeição clínica, apesar de este não poder ser documentado, se inicie a anticoagulação terapêutica. Na COVID-19, alguns estudos sugerem que os níveis de D-dímeros poderão ser o parâmetro mais importante na decisão terapêutica em anticoagular e não tanto a presença de embolismo pulmonar relatado na angio-TC.[6] Há menor acuidade diagnóstica do EP em angio-TCs de qualidade subótima, com artefactos, habituais nos exames urgentes, sendo que na COVID-19 ocorre primordialmente trombogénese microvascular pulmonar.

Deste modo se entende o apelo de agências internacionais para uma necessidade de maior critério, quer na requisição quer na protocolização das TCs, para minimizar os efeitos da exposição cumulativa à radiação ionizante, sobretudo nos casos de (re)avaliações por vezes seriadas e multifásicas (sem e com contraste).

CONTRIBUTO DOS AUTORES

CFS: Pesquisa bibliográfica, elaboração do primeiro rascunho do manuscrito.

RMF: Revisão crítica.

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