

The Role of Nutritional Care in Sickle Cell Disease: A Real Phenomenon

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Abstract

Despite the role of nutrition in Sickle Cell Disease (SCD) being researched for over 60 years, nutrition in SCD remains under recognised and under used in the management of the disease. The nutritional care needs inherent in sickle cell patients remains poorly recognised and therefore under treated. Nutrition in SCD is an untapped and under researched area in Dietetics. This has resulted in poor dietetic involvement, poor knowledge and understanding of nutritional implications of SCD and a lack of nutritional guidelines and standards of care. Dietitians are however, recognised as nutrition and diet experts in managing the malnutrition risk of susceptible patients.

Both malnutrition and SCD are now considered a global public health problem with a significant cost and disease burden associated with it. Furthermore, SCD can be contributing to the overall malnutrition cost burden and its inherent malnutrition risk can be adding to the morbidity and mortality of the condition. There is empirical data to suggest a link between the pathophysiology of SCD and under nutrition, referred to as Disease- Related Malnutrition (DRM). Under nutrition, synonymous with malnutrition, is identified as a critical feature and significant complication of SCD. Dietitians can therefore play a pivotal role in improving nutritional health outcomes of patients with long term conditions including sickle cell patients. The paper therefore explores the merit of the role of the Dietitian in treating DRM in SCD.

Keywords: Nutritional Care; Disease-Related Malnutrition; Sickle Cell Disease; Dietitian

Introduction

The nutritional care needs inherent in Sickle Cell Disease (SCD) is under recognised in the United Kingdom (UK) [1], as awareness and knowledge of the condition is poor [2].

Considering Disease -Related Malnutrition (DRM), as a real phenomenon in SCD is feasible, as SCD is theorised to produce a form of 'protein energy malnutrition' [3]. Additionally, under nutrition in SCD, is seen as both a 'critical feature' and a 'serious complication' of the disease [4]. The ambition is that this correlation with DRM will provide a fresh perspective on the 'authentic' and 'unique' nutritional needs of this nondescript population. Maintaining the status quo counteracts the critical point raised by The European Nutrition for Health Alliance [5]; 'access to a safe and healthy variety of food, is a basic human right'. It is a basic human right for SCD patients, with or at risk of DRM, to have access to a Dietitian (nutri-

tion and diet expert), to manage their nutritional risks, warranting an urgent need for change in policy and practice.

Consequently a clear paucity of policy and practice in the provision of nutritional services in SCD in the UK [6], confounds the need to undertake a study to explore the gross lack of awareness and knowledge of nutrition in SCD. The study is aimed at improving the knowledge of service users and stakeholders involved in providing care to sickle cell patients. The study will emphasise the role of under nutrition associated with SCD and the valuable role Dietitians can play to improve the nutritional care provision in SCD. The recent launch of the pioneering Nutrition in SCD Standards of Care in the UK (a subsection of the National Standards for the Clinical Management of Adult SCD patients in the UK) [2], provides empirical evidence to support such an enquiry into the role of the Dietitian in SCD.

The growing prevalence observed in both DRM [7] and SCD [1], although disproportionate, compels further attention be paid to effectively recognise and address the ensuing health and financial consequences of both conditions. Highlighting DRM as a real phenomenon in SCD doesn't help to ease this economic burden on National Health Service (NHS) resources; but neglecting to acknowledge its existence will perpetuate the status quo and negate the need to improve the role of nutritional care in SCD. Failing to acknowledge the link between the pathophysiology associated with SCD and under nutrition will only add to the cost and disease burden of SCD which is a growing occurrence is. By recognising the DRM risk of SCD, it is possible to forward plan for the infrastructure needed to effectively address this growing problem in SCD [8].

To date the role and importance of nutrition in SCD is still unfolding [9]; the occurrence of the risk of DRM in SCD an even bigger unknown in the wider SCD research context, however there are lessons to be learnt from organisations such as the European Nutrition for Health Alliance [5]. This organisation is an exemplar for change, providing clear developmental aspirations to help shape the vision for change. For sickle cell this means, advocating for nutrition in SCD to be placed on the political agenda, for nutrition in sickle cell to become a part of the 'required clinical care' of the condition [4] and being open to innovative models of nutritional care interventions tailored to SCD, which are integrated in the wider sickle cell landscape.

What is Sickle Cell Disease?

SCD is the most common and fastest growing autosomal recessive blood genetic disorder in the UK [2] and around the globe [10] making it to be one of the most important single gene disorders in human beings [11]. In SCD, haemoglobin (Hb), the oxygen carrying molecule present in red blood cells, is defective and when deoxygenated becomes rod like, deformed and sickle shaped. The disorder results from a mutation in the 6th codon of the 11th chromosome of the β globin chain in which the amino acid valine is substituted by glutamine resulting in the sickle cell haemoglobin (HbS) [12]. The most common genotype is homozygous SS disease, while S-Haemoglobin C (SC) disease, S β + thalassemia and S β 0 thalassemia are also relatively common [13].

Aliyu, Tumblin and Kato [14] describe a number of pathophysiological events resulting in vaso-occlusion. These pathophysiological events result from abnormalities in the structure and function of hemoglobin, red blood cell membrane integrity, erythrocyte density, endothelial activation, microvascular tone, inflammatory

mediators, and coagulation. Aliyu, Tumblin and Kato [14] have categorized the pathophysiologic events into four general categories: anemia and its sequelae; vaso-occlusive crises and bone marrow fat embolization syndrome; infection (from functional asplenia) and organ dysfunction.

The life span of the affected tissues and organs [15] causing organ damage is identified by Aliyu, Tumbilin and Kato [14] to result from a combination of hemolysis and infarction which may present as stroke, retinopathy, nephropathy, liver disease or pulmonary arterial hypertension. SCD is considered as a multisystem condition which involves the main organs and systems including the skeletal, genito-urinary, gastrointestinal, spleen, hepatobiliary, cardiopulmonary and central nervous systems [16,17].

The hallmark clinical manifestation of SCD is the acute vaso-occlusive event or painful episode [13] which is the main reason for emergency room visits and hospitalisations [18,19]. This unique type of pain can start as early as 6 months of age, recur unpredictably over a lifetime and require treatment with opioids [20]. Painful events are also a measure of disease severity and predictor of early death in adults [21].

There are a wide range of factors which precipitate a sickle cell crisis including; hypoxia, acidosis, dehydration, infection, extreme fatigue, trauma, temperature changes (sudden), stress/anxiety and increase physical/physiological demand such as pregnancy, physical exercise [17,22]. In most cases, SCD crisis requires immediate hospitalising and treatment with anti-inflammatory drugs, non-steroidal analgesics, hydroxyurea, opioid analgesia, rehydration and in severe cases transfusion, which may cause other long-term side effects [13].

What is Disease-Related Malnutrition?

Frequently, the term 'malnutrition' is synonymously used with the term 'under nutrition [23]. It is very commonly defined as 'a state of deficiency or excess (or imbalance) of energy, protein and other nutrients which causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome [24]. In developed countries, disease which can be acute or chronic, is found to be the main cause of malnutrition [25]. As a result, malnutrition which results from disease, is commonly known as Disease-Related Malnutrition (DRM).

DRM has been identified in the literature as being under recognised, across a wide range of healthcare settings [26], despite the serious consequences manifested which includes wide organ sys-

tem damage, its effect on the psychological health and the cumulative impact it has on the morbidity and mortality of those affected [27]. Adding to the clinical cost of DRM, is the financial costs, which forms the basis for the reasons why DRM should not be ignored. This is evident in the increased treatment and healthcare utilisation costs associated with DRM [28,29].

A number of factors may result in or aggravate DRM [30], which are relevant to the SCD patient population including, response to trauma, infection or inflammation, altering metabolism, appetite, absorption, or assimilation of nutrients. A number of drug related side effects from drugs such as chemotherapy, morphine derivatives, antibiotics, sedatives, neuroleptics, digoxin and anti-histamines, may cause anorexia or interfere with the digestion of food, resulting in DRM [28]; many of these drugs are used to treat the clinical features of SCD [2].

Who is at risk?

DRM is a common problem in patients with chronic or severe diseases [28]. Very commonly patients with poor intake or appetite, with dysphagia, chronic disease, or poor functional and social or cognitive ability are more likely to develop DRM [31]. The non-disease contributing factors of DRM include, those affected by social segregation, psychological factors, economic status, lack of medical awareness and those with extended hospitalisations [32].

In the case of patients suffering with SCD, they can be considered within the group of patients at risk of DRM. SCD itself is a chronic long-term condition, characterised by the hall mark sickle cell crisis which invariably requires frequent emergency hospital admissions and costly treatment costs [18]. There are therefore clear disease and cost burden benefits for those patients at risk of DRM (including SCD patients) who are fed alongside receiving medical treatment for their underlying disease [35].

What are the causes of DRM?

The role of cytokines, glucocorticoids, peptins, insulin and insulin like growth factors which are secreted in response to appetite reduction, is identified as the single most important factor causing DRM [36]. Continued inflammation, a chronic feature of SCD [16], has been identified to play a significant role in the suppression of appetite observed after recovery, with a knock-on effect on the restoration of weight loss and functional capacity in affected patients [25].

What are the consequences?

The consequences of DRM have been identified in the literature to include the following: shorter survival rates, lower functional capacity, longer hospitalisation, increased complication rates, and higher drug prescription rates [27]. A number of these factors are relevant to the SCD patient population. In addition, frailty, unintentional weight loss, weakness, immobility, sarcopenia and poor endurance are further consequences of malnutrition [33] emphasising the costly, clinical and financial impact of DRM, if left untreated. This is extremely important for people living with Long Term Conditions (LTC's), which includes SCD, as it is a chronic disease requiring ongoing medical and pharmacological treatment [35], however there are currently no SCD specific nutritional related cost data available due to the poor recognition of the role of nutrition in SCD.

Significantly, malnutrition affects the function and recovery of every organ system [23]. SCD is a blood disorder with multi-organ/system involvement as described by [16] Alexandre and Yahya [17]. The significance of the similarities between SCD and DRM is evident in the main clinical features observed in DRM. Norman, *et al.* [28] identified the impaired immune function, delayed wound healing, convalescence from illness, and decreased functional status (including loss of muscle function), as the main contributors for the enhanced morbidity observed in malnutrition.

According to the British Association of Parenteral and Enteral Nutrition (BAPEN) and Elia [36], managing malnutrition is seen as a major resource issue for public expenditure. Recent calculations reveal that the associated costs of DRM in 2015/16 in the UK is among £19 billion [36]. The cost at individual level is the following; those with or at risk of malnutrition is £7,408 compared to £2,155 for non-malnourished patients [36].

The role of the Dietitian in the treatment of Disease-related-Malnutrition in Sickle Cell Disease

Dietitians have been identified to play a fundamental role in the management (treatment and prevention) of malnutrition in major LTCs such as Cancer and COPD [37]. Part of their involvement is to raise awareness of the risk of malnutrition and effectively manage the DRM associated with LTCs. The malnutrition policy of the British Dietetic Association (BDA)[38], emphasises the importance of providing good nutritional care by Dietitians to reduce the effects of malnutrition in the most susceptible population groups. Dietitians are recognised as diet and nutrition specialists and therefore

key players in the nutritional management of malnutrition. There is therefore merit in considering the lack of Dietetic input in SCD which may potentially be contributing to the perpetuation of the under recognition and under treatment of the DRM risk in SCD. Furthermore, there is clear evidence to the lack of translation of existing empirical data from previous research into the role of nutrition in SCD observed in the lack of availability of nutritional management guidelines in SCD [2].

However, neglecting to forward plan for policy development to improve the QOL and nutrition outcomes of the SCD population [8] in the UK would have serious repercussions. Nutrition in SCD is on the rise but knowledge and awareness of both nutrition in SCD and SCD, remains poor in the UK [1,2]. The new National Clinical Standards for Adult Sickle Cell patients in the UK however, aims to reform SCD management to include nutritional care [2]. The Nutrition Standards for SCD [2], calls for Dietitians to manage the nutritional consequences of a fast turnover of Red Blood Cells (RBC) in SCD, as part of the multidisciplinary team caring for sickle cell patients and recognises the need for patient and healthcare provider engagement. The Nutrition Standards build on the empirical data from the research exploring the role of nutrition in SCD, which has been in existence for over 60 years according to the review article by Hyacinth, Gee and Hibbert [4].

The first and most direct study to show a positive correlation between clinical improvement following a dietary intervention proved to be pivotal in identifying the benefit of protein and energy supplements to improve the clinical status and growth in children with SCD [39]. The findings reported by the Heyman, *et al.* study in 1985 [39], in which the researchers studied 5 growth-stunted children with the severe form of SCD, each falling below the fifth percentile for both weight and height, showed clinical improvement and accelerated growth in two of the subjects. The diet of the study sample was supplemented with protein and calories which was fed to them via a naso-gastric feeding tube, in addition to their regular dietary intake. The results showed that protein and energy supplements could improve clinical status and growth in children with SCD. The Heyman study [39] also underlines the fact that vitamin and mineral supplements alone had no effect on the clinical status or growth which means that the positive effect was as a result of the protein and calories supplemented in the diets of the subjects.

Important to note is the fact that there are still currently no spe-

cial dietary recommendations for protein and/or energy for SCD patients, despite the large body of data available [3,4]. The study conducted by Tomer, *et al.* [40], where SCD men were given omega 3 (n-3) fatty acids supplements have shown clinical improvements relating to significant reductions in inflammation, oxidative stress, red cell density and pain episodes, and improved microvascular function. A more recent study conducted by Daak, *et al.* [41], amongst Sudanese SCD patients, found positive reductions in the median rate of clinical vaso-occlusive events, severe anemia, blood transfusion rates and white blood cell counts. Overall the findings of the study suggest omega-3 fatty acids can be an effective, safe and affordable therapy for SCD however the findings need to be verified in a large multicenter study. Both studies [40,41] provide some evidence base for Dietitians to consider the use of omega 3 (n-3) fatty acids to improve the nutritional outcomes in adult sickle cell patients, in turn possibly improving the health outcomes in susceptible patients, which may have significance in future cost and disease burden in SCD.

However, despite all this evidence, the nutritional needs of sickle cell patients are still under recognised and under treated [1]. What we do know however, from the available empirical data is that under nutrition is identified as a serious complication of SCD [4] highlighting a link between the pathophysiology of the disease and under nutrition. The question we are left with is to explore more explicitly the relevance and significance of this link between undernutrition and SCD to improve the under recognition of the role of nutrition in SCD. The literature describing malnutrition in SCD does not however link the pathophysiology of SCD directly to the occurrence of malnutrition in SCD leaving a clear gap in knowledge. The potential benefit of linking the disease-related pathophysiology of SCD to the malnutrition in the condition, will however improve the understanding of the effects of the disease on the nutritional risk of the patients and help Dietitians to better understand the nutritional implications of SCD.

In addition, Dietitians provide nutritional assessment including assessing the patients risk of weight loss, improving nutritional intake and nutritional status, vital prerequisites for better patient outcomes and enhancing QOL [42]. According to the British Dietetic Association (BDA) + British Specialist Nutrition Association (BSNA) [37] this can be achieved with increased Dietetic involvement in patient care. However, due to the scale of the problem, the role of non-Dietitians should not be discounted [42]. On the con-

trary, this could reduce the under recognition of DRM if everyone involved with chronic disease management is encouraged to have a conversation about the patient's diet, any changes in appetite, interest in food or if they've lost weight unintentionally [42].

Identifying the specific DRM risk variables in SCD is a key factor to help raise awareness of malnutrition in SCD and help tailor the nutritional advice and treatment given by Dietitians. The main clinical features, in other words the pathophysiology of SCD, characterised by chronic haemolysis causing chronic fatigue and anaemia and vaso-occlusion which causes the painful sickle cell crisis, chronic inflammation and poor immune function, can cause the malnutrition experienced by sickle cell patients [14]. It is these disease-related clinical features of SCD which therefore result in the DRM risk in SCD. However, it has already been established that malnutrition caused by disease is known as DRM [25] whether chronic or acute. The relevance of understanding the link between nutrition and SCD directly impacts the under recognition of malnutrition which in turn can be directly linked to the increased healthcare usage in affected patients, evident in the cost and disease burden associated with both SCD and DRM [28].

Sickle cell crisis, the hallmark feature of SCD is identified as the main reason for hospital admission in SCD [13]. The healthcare costs associated with SCD represents a significant cost for commissioners and the National Health Service in the UK [43]. In 2010–11, England had 6077 admissions associated with SCD with crisis as primary diagnosis [43]. The retrospective study undertaken by Pizzo, *et al.* [44] identified a total cost for commissioners of ~£19 million for hospital admissions in England between 2010 and 2011, for crisis as the primary diagnosis. Factoring in the cost associated with the DRM risk in SCD will significantly increase the economic burden in SCD, which is one of the reasons why the World Health Organization (WHO) [45] has deemed SCD as a public health problem. The economic burden associated with SCD is directly linked to its pathophysiology as seen in sickle cell crisis and the DRM risk associated with the condition. This makes a compelling case in support of finding appropriate Dietitian led nutritional strategies to address the DRM risk associated with SCD.

Conclusion

SCD is a devastating condition and addressing the nutritional care needs of the SCD population, by increasing dietetic input in SCD, can significantly improve the health outcomes and quality of life of this patient population- good nutrition is a basic human

right and Dietitians can be change makers in this emerging speciality. Learning from and considering other examples provided in the literature, it is clear that proper nutritional care has shown a clear reduction in the prevalence of hospital malnutrition and costs.

Therefore, linking the pathophysiology associated with SCD and nutrition is a positive step to help raise awareness of the DRM risk inherent in SCD. Recognising the DRM risk in SCD will help raise awareness amongst Dietitians who are recognised to be the nutrition and diet experts in effectively managing the nutritional risks in susceptible patients. Dietitians can play a pivotal role in raising awareness of the nutritional risk associated with the clinical features of SCD but moreover contribute to the development of nutritional guidelines building on the National Nutrition Standards of care in SCD.

The answers perhaps lay in the conclusions drawn from the evidence-based document produced by the BDA and BSNA, which documents the benefits of Dietitians providing good quality nutritional care. The role and involvement of Dietitians have been shown to positively impact on the QOL of those living with LTC's. Dietetic support ensures optimal nutrition for those living with LTC's including the sickle cell population. It is well known that some LTC's can have a detrimental impact on patient's overall nutritional wellbeing/status; failing to address the DRM risk in SCD may be contributing to the disease and cost burden associated with the disease.

Bibliography

1. Matthews C. "Sickle cell disease: on the rise but under-recognised". *Dietetics Today* (2014/15): 24-27.
2. Sickle Cell Society. "Standards for the Clinical care of adults with sickle cell disease in the UK". London: Sickle Cell Society (2018).
3. Hyacinth H., *et al.* "Malnutrition in sickle cell anaemia: Implications for infection, growth and maturation". *The Journal of Applied Behavioral Science* 7.1 (2013): 1-11.
4. Hyacinth H., *et al.* "The role of Nutrition in Sickle Cell Disease". *Nutrition and Metabolism* 3 (2010): 57-67.
5. The European Nutrition for Health Alliance. From Malnutrition to Well nutrition: policy to practice. A report of the European Nutrition for Health Alliance, 2nd Annual Conference: Brussels. (2006).
6. Matthews C. "Pioneering nutrition services for sickle cell disease". *Dietetics Today* (2016): 24-26.

7. Amaral T, *et al.* "The economic impact of disease-related malnutrition at hospital admission". *Clinical Nutrition* 26 (2007): 778-784.
8. Piel F, *et al.* "Global Burden of Sickle Cell Anaemia in Children under Five, 2010-2050: Modelling Based on Demographics, Excess Mortality, and Interventions". *PLoS Medicine* 10.7 (2013).
9. Khan S, *et al.* "Precipitating factors and targeted therapies in combatting the perils of sickle cell disease- A special nutritional consideration". *Nutrition and Metabolism* 13.50 (2016): 1-12.
10. Weatherall D and Clegg J. "Inherited haemoglobin disorders: an increasing global health problem". *Bull WHO*. 79 (2001): 704-712.
11. Jastiniyah W. "Epidemiology of sickle cell disease in Saudi Arabia". *Annals of Saudi Medicine* 31.3 (2011): 289-293.
12. Adomo E, *et al.* "The beta globin gene cluster haplotypes in sickle cell anaemia patients from North East Brazil: a clinical and molecular view". *Haemoglobin* 28 (2004): 267-271.
13. Asnani M. "Sickle Cell Disease". In: JH Stone, M Blouin, editors. *Inter Enc of Rehab*. (2010).
14. Aliyu Z, *et al.* "Current therapy of sickle cell disease". *Haemoglobin* 91 (2006): 7-10.
15. Chakrovarty S and Williams T. "Sickle cell disease: a neglected chronic disease of increasing global importance". *Archives of Disease in Childhood* 100.1 (2015): 48-53.
16. Meshikhes A and Al-Faraj A. "Sickle cell disease and the general surgeon". *Journal of the Royal College of Surgeons of Edinburgh* 43 (1998): 73-79.
17. Alexandre A and Yahya E. "Perioperative Precautions and Management of Sickle Cell Anaemia: A Literature Review". *Rep and Opinion* 7.9 (2015).
18. Ballas S and Lusardi M. "Hospital readmission for adult acute sickle cell painful episodes: frequency, aetiology and prognostic significance". *American Journal of Hematology* 79 (2005): 17-25.
19. Ballas S, *et al.* "Sickle cell pain: a critical reappraisal". *The American Society of Hematology* 120.18 (2012): 3647-3656.
20. Smith W, *et al.* "Understanding pain and improving management of sickle cell disease: The Pisces study". *Journal of the National Medical Association* 97 (2005): 183-193.
21. Steinberg M. "Predicting clinical severity in sickle cell anaemia". *British Journal of Haemoglobin* 129 (2005): 465-481.
22. Brent Sickle cell and Thalassemia Centre. "Sickle Cell for Healthcare Professionals". (2014).
23. Saunders J, *et al.* "Malnutrition and undernutrition". *Medicine* 39.1 (2010): 45-50.
24. Lochs H, *et al.* "Introductory to the ESPEN Guidelines on enteral nutrition: terminology, definitions and general topics". *Clinical Nutrition* 25 (2006): 180-186.
25. Stratton R, *et al.* "Disease-related malnutrition: an evidence-based approach to treatment". Oxford: CABI Publishing (2003).
26. Elia M, *et al.* "To screen or not to screen for adult malnutrition?" *Clinical Nutrition* 24 (2005): 867-884.
27. Freijer K, *et al.* "The economic costs of disease related malnutrition". *Clinical Nutrition* 32 (2013): 136-141.
28. Norman K, *et al.* "Prognostic impact of disease-related malnutrition". *Clinical Nutrition* 27 (2007): 5-15.
29. Feldblum I, *et al.* "Nutritional risk and healthcare use before and after acute hospitalisation among the elderly". *Nutrition* 25 (2009): 415-420.
30. Campbell I. "Limitations of nutrient intake. The effect of stressors: trauma, sepsis and multi organ failure". *European Journal of Clinical Nutrition* 55.1 (1999): 143-147.
31. Leach R, *et al.* "Nutrition and fluid balance must be taken seriously". *British Medicine Journal* 346 (2013): 1-5.
32. Waitzberg D, *et al.* "Hospital malnutrition: the Brazilian National survey: a study of 4000 patients". *Nutrition* 17 (2001): 575-580.
33. Isabel M, *et al.* "The impact of malnutrition on morbidity, mortality, length of hospital stays and costs evaluated through a multivariate model analysis". *Clinical Nutrition* 22 (2003): 235-239.
34. Langhans W. "Anorexia of infection: current prospects". *Nutrition* 16 (2000): 996-1005.
35. Department of Health. "Long term conditions Compendium of Information". Third Edition. (2013).

36. Elia M on behalf of the malnutrition Action Group of BAPEN and the National Institute for health research Southampton Biomedical Research Centre. "The cost of malnutrition in England and potential cost savings from nutritional interventions". BAPEN and National Institute for Health Research. (2015).
37. British Dietetic Association and British Specialist Nutrition Association. "The Value of Nutritional Care in Helping the NHS to Deliver on the NHS Outcomes Framework: An assessment of how delivering high quality nutritional care can enhance the quality of life for people with long-term conditions" (2013).
38. British Dietetic Association. "The Management of Malnourished Adults in All community and all Health and Social Care Settings: Malnutrition Policy Statement. Birmingham: British Dietetic Association". (2017).
39. Heyman., *et al.* "Growth retardation in sickle-cell disease treated by nutritional support". *The Lancet* 325.8434 (1985): 903-906.
40. Tomer A., *et al.* "Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids". *Journal of Thrombosis and Haemostasis* 85.6 (2001): 966-974.
41. Daak AA., *et al.* "Effect of omega-3 (n-3) fatty acid supplementation in patients with sickle cell anemia: randomized, double-blind, placebo-controlled trial". *American Journal Clinical Nutrition* 97 (2013): 37-44.
42. Holdaway A and Franklin H. "Working together to tackle malnutrition in the community: rising to the challenge". *CN* 16.3 (2016): 49-52.
43. Aljuburi G., *et al.* "Trends in hospital admissions for sickle cell disease in England, 2001/02-2009/10". *Journal of Public Health* 34.4 (2012): 570-576.
44. Pizzo E., *et al.* "A retrospective analysis of the cost of hospitalisation for sickle cell disease with crisis in England, 2010/11". *Journal of Public Health* 37.3 (2014): 529-539.
45. World Health Organisation. "Sickle-cell Anaemia: Report by the Secretariat". (2006).

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