Metabolic syndrome among adults living with sickle cell disease

Foluso Joy Ogunsile⁎, Shawn M. Bediako, Julie Nelson, Cody Cichowitz, Tiffany Yu, C. Patrick Carroll, Kerry Stewart, Rakhi Naik, Carlton Haywood Jr, Sophie Lanzkron

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ABSTRACT

Metabolic syndrome (MetS) is a key risk factor for cardiovascular disease (CVD) incidence and all-cause mortality. MetS prevalence among adults with sickle cell disease (SCD) is not well known. We report initial findings from a cross-sectional study that examined MetS risk factors within a cohort of adults living with SCD.

50 adult SCD participants (ages 21–66 years; 72% female) completed demographic and health behavior surveys, health-related family and personal histories, and anthropometric and laboratory measurements. Descriptive and inferential statistics were used to summarize and compare CVD risk factors, stratified in separate analyses by SCD genotype and sex.

Triglyceride, blood pressure, and fasting glucose levels were within normal limits. 78% of the cohort reported moderate to high physical activity. However, 46% of this cohort was overweight and dietary saturated fat intake exceeded both the national average (11%) and US Dietary Guidelines (<10%). 14.3% of the cohort fulfilled criteria for MetS with large waist circumference and reduced HDL levels prominently accounting for this status.

We evaluated the prevalence of MetS in a cohort of adults living with SCD. Our findings suggest that increased attention to eating habits and physical activity may generate new approaches for decreasing cardiovascular morbidity in SCD.

Key points

Question:
What is the prevalence of metabolic syndrome in adults with sickle cell disease (SCD)?

Findings:
In this cross-sectional study of 50 adults with SCD, 14% of adults with SCD met criteria for metabolic syndrome. There was a higher prevalence of metabolic syndrome in HbSC disease compared to HbSS disease, but there were no differences between metabolic syndrome between males and females. Despite the prevalence of metabolic syndrome in adults with SCD, interventions to address cardiovascular health are often not implemented due to concerns for complications associated with exercise and preconceptions about longevity in this population.

Meaning:
SCD providers should prioritize screening adults for metabolic syndrome and other cardiovascular risk factors.

1. Introduction

In the United States, obesity rates are rising for people living with sickle cell disease (SCD) and this pattern appears to hold across the life span. While previous findings often underscored growth and weight deficiencies in SCD [1–3], recent evidence indicates an opposite trend. For example, adolescent girls living with SCD are 3 times more likely than boys to be obese [4], and normal weight adult women living with SCD have been reported to have higher levels of adiposity and low fat free mass [5]. In a recent study examining weight status in 100 adults with SCD, 54% of adults living with SCD were either obese or overweight [6]. Another longitudinal study of weight status in adult women with SCD noted an average increase in BMI of 8 kg/m² over ten or more years. Furthermore, 28% of these women were obese and the remaining 62% of these women were overweight at the conclusion of this study [7].

The increasing rates of obesity in SCD are perhaps exacerbated by the fact that the life span of SCD patients has increased considerably over the past three decades. Median life expectancy for persons living
with SCD is now well into the fifth decade, compared to the 1970’s, when median life expectancy was reported to be <20 years [8–10]. As adults living with SCD grow older, their overall health profile faces exposure to many of the same risks that also affect the broader, aging population – namely, sedentary lifestyles and poor eating habits. Thus, an aging SCD population, already at increased risk for stroke, could be at increased risk for developing CVD, the leading cause of mortality in the United States.

Metabolic syndrome (MetS) is a group of risk factors such as visceral obesity, hypertriglyceridemia, and hyperglycemia that is associated with a two-fold and ten-fold risk of developing CVD and type II diabetes, respectively [11]. Individuals with MetS have a 46% increase in all-cause mortality compared to individuals without MetS [12]. Furthermore, a comparative risk assessment study in the US showed that poor dietary habits and sub-optimal intake of fruit, vegetables, and omega-3 fatty acids independently contribute to all-cause cardiovascular mortality by 45% [13].

In this cross-sectional study, we sought to determine the prevalence of MetS and CVD risk factors in a cohort of adults with SCD and, subsequently, their risk factors for developing CVD.

2. Methods

Fifty participants were recruited from a comprehensive adult sickle cell center at a large, urban academic medical center located in the mid-Atlantic region of the US. Individuals were approached either before or after their wellness visits and informed about the nature of the study. Those who expressed interest in the study were consented per an IRB-approved protocol and were scheduled for an appointment in the institution’s General Clinical Research Center, where they completed questionnaires, laboratory testing, and anthropometric measurement. The questionnaires surveyed information about participants’ personal and family cardiac histories, smoking and alcohol consumption, fatigue, general pain, nutritional intake, medication use, physical activity and stress. A comprehensive metabolic panel, complete blood cell count, C-reactive protein, lipid panel, fasting glucose and fructosamine levels were collected from all participants. Of note, glycated hemoglobin, hemoglobin A1C, is not a reliable test for the diagnosis of diabetes mellitus in SCD [14]. Hemoglobin A1C is a measure of the average glucose levels over the preceding 2–3 months. Due to the shorter life span of red blood cells in SCD, hemoglobin A1C levels are often inaccurate in this population [15]. Instead, alternative methods for diagnosing diabetes mellitus should be used in SCD, such as having a fasting glucose >125 mg/dL or a random glucose level >200 mg/dL with symptoms. Fructosamine tests, a measure of serum glycated protein, offer a more accurate measure of glycemic control than hemoglobin A1C in patients with SCD as it is not affected by the life span of red blood cells [16]. Unfortunately, fructosamine tests are not standardized, the relationship of fructosamine tests to serum glucose levels has not been validated, and fructosamine measurements are not currently an approved diagnostic criterion for diabetes mellitus [16].

We examined both fasting glucose and fructosamine levels in our participants as both tests provide valuable information about glycemic control in this population. We used the National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III) to assess MetS and control in this population. We used the National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III) to assess MetS and control in this population. We used the National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III) to assess MetS and control in this population.

2.1. Waist circumference

Participants met this criterion for MetS if their waist circumference exceeded 89 cm (for females) or 102 cm (for men).

2.2. Triglycerides

Participants met this criterion for MetS if their triglyceride level was >150 mg/dL.

2.3. High-density lipoprotein

Participants met this criterion for MetS if their HDL level was <50 mg/dL for women and <40 mg/dL for men.

2.4. Blood pressure

Participants met this criterion for MetS if their systolic blood pressure exceeded 130 or if their diastolic blood pressure exceeded 85.

2.5. Fasting glucose

Participants met this criterion for MetS if their glucose level was >100 mg/dL.

3. Data analytic approach

Differential and inferential statistics (one-way ANOVAs and chi-square analyses) were used to compare MetS components based on SCD genotype and sex.

4. Results

One female participant was pregnant and, consequently, was excluded from our analysis. Thus, the final cohort consisted of 35 females (mean age = 39.3 years) and 14 males (mean age = 41.6 years). Thirty-one participants had hemoglobin SS disease (Hb SS) and 18 had hemoglobin SC disease (Hb SC).

As shown in Table 1, 14.3% of our cohort fulfilled criteria for MetS. In comparison, the age-adjusted prevalence of metabolic syndrome in African Americans in the US is 27% (p = .045, 95% CI 5.95 to 27.26) [12].

Reduced HDL levels and larger waist circumferences were the most commonly observed risk factors and were present in 69.4% and 44.9% of our cohort, respectively. Risks for fasting glucose (6.1%), triglycerides (8.2%), and systolic blood pressure (12.2%) were observed at lower rates (also shown in Table 1). As shown in Table 2, we observed an overall difference in MetS based on genotype (Hb SS = 6.5%, Hb SC = 27.8%, p < .10). Hb SC participants had larger waist circumference and higher fasting glucose level compared to Hb SS participants. In contrast, participants with Hb SS had lower HDL compared to Hb SC participants. Table 3 indicates that there was no statistically significant difference in mean fasting glucose levels between genotype groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean value (SD)</th>
<th>Proportion at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>41.6 (10.76)</td>
<td>Female n = 35</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>96.53 (21.99)</td>
<td>90.75 (14.05)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>114.21 (57.22)</td>
<td>83.36 (36.21)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>35.07 (9.51)</td>
<td>51.30 (20.31)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>115.79 (15.00)</td>
<td>108.59 (13.15)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>69.11 (8.99)</td>
<td>62.17 (6.18)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>86.50 (8.07)</td>
<td>80.91 (13.73)</td>
</tr>
<tr>
<td>Metabolic syndrome MetS</td>
<td>28.6%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

* “Risk” is defined as: waist circumference > 89 cm (Females) and >102 cm (Males); triglycerides levels > 150 mg/dL; HDL < 50 mg/dL (Females) and < 40 mg/dL (Males); systolic blood pressure > 130; diastolic blood pressure > 85; fasting glucose levels > 100 mg/dL.
significant difference for overall MetS as a function of sex (male = 28.6%, female = 8.6%, p > .10), although males were more likely to have higher triglycerides (p < .05).

The cohort’s profile with respect to CVD risk factors was mixed and is shown in Table 4. Approximately 34.7% of our participants had a history of smoking cigarettes (9 pack years, on average), and 18% were smoking cigarettes currently. About 22.4% of our participants had a positive family history for CVD, and 31.4% of participants met inactivity criteria of the International Physical Activity Questionnaire (IPAQ). One participant reported a history of diabetes and only 6.3% were observed to have elevated fasting glucose levels. However, fructosamine levels satisfied criteria for diabetes in 14.2% of our participants and for pre-diabetes in 67.3% of our participants. Eighty percent of participants received medical treatment for hypertension (not shown in Table 4).

None of the participants were underweight and all participants had BMI values > 18.5 kg/m². Twenty percent of our participants were overweight and had BMI values between 25 and 30 kg/m² (Hb SS = 4 participants; Hb SC = 6). 26% of our participants had BMI values > 30 kg/m² and were obese (Hb SS = 4 participants; Hb SC = 7; Hb S Beta thalassemia = 2). Two of the Hb SC participants were morbidly obese with a BMI > 40 kg/m².

Dietary saturated fat and sugar intake exceeded the national recommendations for daily allowance. The American Heart Association recommends 11 to 13 g of saturated fat (based on a 2000 cal diet) and also recommends that total daily fat intake should not exceed 35% of daily calories. Our participants consumed a daily average of 26 g of saturated fat and 36% of their daily diet consisted of foods high in fat (Table 4). Daily sugar intake was also higher than the recommended 2–3 servings based on a 2000 cal diet; participants consumed 3.84 servings of dietary fat, sweets, and oil per day (Table 4).

5. Discussion

Very few studies have evaluated CVD risk factors in adults with SCD. We found that 14.3% of our participants met criteria for MetS and, consequently, are at higher risk for developing both CVD and DM. In addition, we observed several affiliated CVD risk factors in this cohort: smoking; pre-diabetes; family history of CVD; obesity and morbid obesity; and diets high in saturated fat. These factors pose additional risks for increasing this population’s all-cause mortality [12].

The current life expectancy for adults with sickle cell anemia (SCA) is 42 for males and 48 for females and is higher for adults with Hb SC disease. The life expectancy for males and females with Hb SC is 60 and 68 years, respectively [18]. The prevalence of MetS increases with age and the highest prevalence occurs in adults over the age of 50 [19]. Unfortunately, due to sedentary lifestyles and poor eating habits in the United States, MetS is increasingly prevalent in children, adolescents and young adults [20]. The prevalence of MetS in adults between 18 and 39 years of age has been reported to be 5 to 18.3% based on NCEP:ATP III guidelines [21,22]. Several of the MetS-related complications, such as diabetes, stroke and coronary artery disease, occur in the fifth and sixth decade of life [23–25]; however, studies report CVD complications and diabetes occurring within 2 to 15 years from the diagnosis of MetS [26]. In addition, the presence of MetS increases all-cause mortality and morbidity in the absence of clinical CVD [27]. Though the life expectancy of adults with SCD remains lower than the general population [28], adults with SCD are living long enough to acquire MetS risk factors and develop MetS-related complications in their lifetime. This possibility is even higher for adults with Hb SC disease as their life expectancy approaches that of the general population [18,28].

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Metabolic syndrome by SCD phenotype.</th>
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<tbody>
<tr>
<td></td>
<td>Hb SS n = 31</td>
</tr>
</tbody>
</table>
| Waist circumference risk | 30 (83.9%) | 12 (55.6%) | 4.51*
| Triglycerides risk | 3 (10.3%) | 1 (3.6%) | 0.33 |
| HDL risk | 50 (62.5%) | 32 (42.5%) | 0.11 |
| Systolic BP risk | 3 (10.3%) | 3 (4.2%) | 0.54 |
| Diastolic BP risk | 0 (0%) | 0 (0%) | – |
| Fasting glucose risk | 3 (9.0%) | 1 (1.4%) | 0.33 |
| Metabolic syndrome | 2 (6.5%) | 5 (27.8%) | 4.23** |

* X² statistic p < .05.
** X² statistic p = .08 (Fisher’s exact test).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Metabolic syndrome by sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female n = 35</td>
</tr>
<tr>
<td>Waist circumference risk</td>
<td>45 (75.0%)</td>
</tr>
<tr>
<td>Triglycerides risk</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>HDL risk</td>
<td>24 (69.7%)</td>
</tr>
<tr>
<td>Systolic BP risk</td>
<td>3 (8.8%)</td>
</tr>
<tr>
<td>Diastolic BP risk</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fasting glucose risk</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3 (8.6%)</td>
</tr>
</tbody>
</table>

* X² statistic p = .09 (Fisher’s exact test).

Based on the calculation HbA1C = 0.017 × fructosamine level (mmol/L) + 1.61 (Cohen et al., Diabetes Care 2003).

* Fructosamine levels > 288 mmol/L corresponds to HbA1C > 6.5.
** Fructosamine levels 241–287 mmol correspond to HbA1C < 6.5.

* We were not able to obtain fructosamine and glucose samples from 2 female participants. Mean values are reported with SD.
Our finding of larger waist circumferences in adults with SCD confirms previous studies that show an upward trend in obesity in young adults with SCD [29]. This upward trend in weight status does not appear to occur in other countries where obesity is not as prevalent. For example, a retrospective study comparing anthropometric measurements between a cohort of adults with Hb SS from the United States and Nigeria found that the United States cohort had higher BMI levels [30]. 2.5% (4/155) of the Nigeria cohort was overweight, compared to 22% (39/177) of the United States cohort based on WHO criteria [31]. In comparison, the prevalence of obesity for the general population is reported to be 8 to 22% in Nigeria [31], whereas, the prevalence of obesity in the United States is 39.8% [32]. This finding suggests that the upward trend in weight status for adults with SCD may reflect environmental factors of diet and activity level.

Although participants reported moderate to high levels of physical activity, this finding is inconsistent with the elevated BMIs and waist circumferences observed in this cohort. Exercise and weight management have not typically been priorities for adult SCD primary care, principally because people with SCD have traditionally been underweight and there have been concerns that exercise triggers vaso-occlusive episodes [33]. Despite this concern, limited data exists that supports aerobic exercise and resistance training recommendations for this patient population. As the evidence builds on whether to recommend moderate or intense aerobic exercise and resistance training, health care professionals who care for adults with SCD should perhaps prioritize dietary-based strategies and low-impact, mild aerobic exercise activities for weight management to address the growing rates of obesity in this population.

We noted a higher percentage of metabolic syndrome in participants with sickle variant syndromes (Hb SC, Hb S Beta thalassemia) compared to SCA within our cohort. Sickle variant syndromes historically do not experience as many complications related to severe hemolysis as in SCA [34], and many providers consider patients with sickle variant syndromes to have a milder phenotype of disease [35]. The milder severity of disease in sickle variant syndrome would explain the improved weight and nutritional status in sickle variant syndromes compared to SCA and account for the higher percentage of metabolic syndrome we found in participants with sickle variant syndromes. Unfortunately, we did not collect hematological markers of hemolysis in our study. Thus, we are not able to comment on a relationship between the degree of hemolytic anemia and the development of metabolic syndrome.

Our study is limited by the fact that the cross-sectional design and relatively small sample size do not allow us to establish a causal relation between MetS and the development of CVD. Further, although MetS diagnostic criteria has been validated by various medical associations and is commonly used in clinical practice to assess CVD risk [36–39], we note that the link between MetS and CVD has not been studied in SCD. In addition, MetS primarily increases the risk for CVD by promoting atherogenesis [40]. Prior studies show that adults with SCD have a lower prevalence of atherosclerotic disease and may even be protected from developing atherosclerosis [41,42]. The lower prevalence of atherosclerotic disease in SCD has been attributed to heightened cholesterol utilization from increased red cell turnover and upregulation of HMOX1, an essential enzyme in heme catabolism linked to preventing atherosclerosis [41]. However, SCD disease-modifying therapies, such as hydroxyurea, has altered the clinical course of SCD and adults with SCD experience decreased hemolysis, fewer hospitalizations and higher baseline hemoglobin levels [43]. As patients with SCD experience decreased hemolysis and higher baseline hemoglobin levels, the presumed protective effect from atherosclerotic disease could become negated and put adults with SCD at an increased risk for developing atherosclerotic disease. Despite uncertainty of the clinical link between MetS and CVD in adults with SCD, our findings nevertheless suggest that it is important for health care providers to consider MetS in adults with SCD because of its relevance to being overweight, obesity, and obesity-related complications.

We note several strengths of our study. First, the use of a well-established protocol to identify MetS permits the potential reproducibility of our findings in other clinic settings. In addition, we used well-validated and psychometrically sound screening instruments to assess dietary habits, daily physical activity, and stress. We balanced the use of these instruments with objective physiological data to minimize the effects of self-reporting bias. Finally, our sample was comprised mostly of adults in their mid-to-late thirties, a relatively underrepresented age in studies with SCD adults.

Our study suggests that as people with SCD live longer, there is an increasing need to address obesity and MetS. Although it is unclear exactly how MetS will contribute to the development of CVD in SCD, the evolving clinical landscape warrants additional studies in obesity, metabolic syndrome and atherosclerotic disease for this population. Our study was limited by the fact that the cross-sectional design and relatively small sample size do not allow us to establish a causal relation between MetS and the development of CVD. Further, although MetS diagnostic criteria has been validated by various medical associations and is commonly used in clinical practice to assess CVD risk [36–39], we note that the link between MetS and CVD has not been studied in SCD. In addition, MetS primarily increases the risk for CVD by promoting atherogenesis [40]. Prior studies show that adults with SCD have a lower prevalence of atherosclerotic disease and may even be protected from developing atherosclerosis [41,42]. The lower prevalence of atherosclerotic disease in SCD has been attributed to heightened cholesterol utilization from increased red cell turnover and upregulation of HMOX1, an essential enzyme in heme catabolism linked to preventing atherosclerosis [41]. However, SCD disease-modifying therapies, such as hydroxyurea, has altered the clinical course of SCD and adults with SCD experience decreased hemolysis, fewer hospitalizations and higher baseline hemoglobin levels [43]. As patients with SCD experience decreased hemolysis and higher baseline hemoglobin levels, the presumed protective effect from atherosclerotic disease could become negated and put adults with SCD at an increased risk for developing atherosclerotic disease. Despite uncertainty of the clinical link between MetS and CVD in adults with SCD, our findings nevertheless suggest that it is important for health care providers to consider MetS in adults with SCD because of its relevance to being overweight, obesity, and obesity-related complications.

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