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Plasma levels of C-reactive protein a cardiovascular risk factor indicator in Sudanese overweight and obese adults.

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Abstract:

Background: ***C-reactive protein (CRP) is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. This study aims to test whether overweight and obesity are associated with low-grade systemic inflammation as measured by serum CRP.***

Methods: ***The study involved 20-60 years old Sudanese adults divided in 3 groups according to their body mass index (BMI). Blood samples were drawn; Serum specimens for the measurement of CRP were analyzed using a high-sensitivity CPR test.***

Results : ***The sample of the present study had included 41 males and 20 females with an age range between 18 and 52 years , the sample was divided into 3 groups according to their BMI into 21 normal weight (BMI=22.17±1.45) , 20 overweight (BMI= 27.68± 1.15) and 20 obese (BMI= 34.15± 3.54) . The normal weight group had the lowest levels of C-reactive protein (2.15 ±2.52 mg/l) and obese the highest (3.95± 2.78 mg/l). Plasma levels of C-reactive protein showed a positive and significant correlation with body mass index (p< 0.05).***

Conclusion: ***In conclusion, this study has shown, in Sudanese adults a positive and significant relationship between levels of CRP and measures of obesity (BMI). These findings suggest a state of low-grade systemic inflammation in overweight and obese persons, the result of this study extend recent observations made by other investigators.***

Keywords:

Obesity; C-reactive protein; Inflammation; Body Mass Index

I. INTRODUCTION

Over the past several decades, the prevalence of obesity has been increasing both in developed and developing countries. It is currently estimated that as much as 20-50% of urban populations in Africa are classified as either overweight or obese, and that by 2025 three quarters of the obese population worldwide will be in non-industrialized countries [1]. Among adults in the in the Eastern Mediterranean region countries the proportion of overweight and obesity among men ranged from 30% to 60%, while among women it ranged from 35% to75%[2].Nationwide data for the status of excess weight in the adult population of Sudan is not available and the true prevalence is not well appreciated.

Obesity is a well-recognized risk factor for various chronic diseases such as cardiovascular diseases, hypertension, and type 2 diabetes mellitus. These conditions lead to reduced quality of life and premature death. Cardiovascular diseases are now the main cause of death in developing countries, being responsible for 42.5% of all deaths, while 20 years earlier they accounted for only 12.4% of mortality [3].

C-reactive protein (CRP) is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages [4] as well as adipocytes[5]. CRP binds to damaged tissue, to nuclear antigens and to certain pathogenic organisms in a calcium-dependent manner. This binding activates the complement system and the interaction of CRP with Fc receptors leads to the generation of proinflammatory cytokines that enhance the inflammatory response. Thus, CRP is thought to act as a surveillance molecule for altered self-antigens and certain pathogens. This recognition provides early defense and leads to a proinflammatory signal and activation of the humoural, adaptive immune system. [6].

Adipose tissue previously was considered a passive storage depot for fat but is now known to play an active role in metabolism. Among the recently discovered compounds expressed in human adipose tissue is the proinflammatory cytokine interleukin 6 (IL-6)[7] . Adipose tissue is estimated to produce about 25% of the systemic IL-6 in vivo. Because of the inflammatory properties of IL-6, the release of IL-6 from adipose tissue may induce low-grade systemic inflammation in persons with excess body fat.

In the last years, an attractive hypothesis has emerged proposing that those cytokines produced by adipose tissue may be responsible for insulin resistance in obesity and, thus, might be involved in obesity-related insulin resistance [8]. Other studies have demonstrated that human adipocytes can produce CRP under the stimulation of several proinflammatory cytokines; moreover, CRP production may be modulated by selected pharmacologic intervention[9].

Inflammation is a known factor in the development of atherosclerosis and subsequent CVD events. Ongoing inflammation increases the vulnerability of an atherosclerotic lesion to erosion or rupture.

CRP concentrations less than 0.05 mg/dL are considered normal; between 0.06 and 10 mg/dL as moderate increases; and more than 10 mg/dL as marked increases. The majority of patients with very high levels have bacterial infection, whereas more moderate degrees of elevation are seen in most chronic inflammatory states.

As a highly sensitive C-reactive protein (CRP) measurement is possible, several large epidemiological studies have demonstrated association between elevated plasma CRP levels reflecting low-grade inflammation and the development of CVD events such as coronary heart disease (CHD), stroke or peripheral arterial disease [10-14]. CRP represents not only a sensitive marker for systemic inflammation, but also contributes to the complex interaction occurring between endothelial dysfunction, lipid accumulation, cell activation and inflammatory response in the pathogenesis of atherosclerosis [15].

Previous studies have suggested that antihypertensive therapy alone may be insufficient to improve endothelial dysfunction in hypertensive patients with high plasma levels of inflammatory markers. Additional therapy to target inflammation may be necessary to improve endothelial function and to prevent progression of coronary atherosclerosis in high-risk hypertensive patients with subclinical inflammations.

The increasing prevalence of cardiovascular diseases in Sudan calls for more attention to this problem, needing more researches on ways of prevention and treatment of this silent disease.

This study aims to test whether overweight and obesity are associated with low-grade systemic inflammation as measured by serum C-reactive protein (CRP) level.

II. MATERIALS AND METHODS:

This study is a Prospective community wise Case-control study. The study was conducted in different centers in Khartoum , cases and control volunteers were looked for in different institutes ,factories , universities and health care centers .The study involves 20-60 years old Sudanese adults divided in three groups according to their body mass index (BMI) into Overweight (20) adults with BMI between 25 to 30 and Obese (20) adults with BMI more than 30 and a well matched Normal weight(21) group of healthy adults with BMI less than 25.

Both cases and control volunteers were consulted about their will to participate in the study, written consent was taken and a structured questioner was given to each of them to get information about age, origin, occupation, and residence.

Children younger than 20 years, persons aged 60 years or older , smokers , alcohol consumers , persons known to have cardiovascular diseases , inflammatory diseases (chronic bronchitis, asthma, emphysema, and rheumatoid arthritis or having common cold) , diabetes mellitus , hypertension , pregnant ladies , persons taking aspirin , statins , antidiabetics, oral contraceptive pills , postmenopausal hormonal therapy were all excluded from the study as all these are known as confounding factors that may affect the level of C- reactive protein .

Body weight and height was measured using standardized procedures. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and used as an indicator of body fat. The 1998 WHO clinical guideline was used to define overweight (BMI, 25-29.9 kg/m^2) and obesity (BMI $\geq$30 kg/m^2).

Blood sample of 5 ml was drawn in empty containers, Serum specimens for the measurement of CRP were prepared by centrifugation and stored to be analyzed. C-reactive protein was analyzed using a high-sensitivity CRP test.

Data analysis was performed using the SPSS 19.0 for Windows software package (SPSS, Chicago, IL) and a P-value of <0.05 was considered as an indicative of a statistically significant difference. .

III. RESULTS

The sample of the present study has concluded 41 males and 20 females with an age range between 18 and 52 years old , the sample was divided into 3 groups according to their body mass index into 21 normal weight (BMI=22.17±1.45) , 20 overweight (BMI= 27.68± 1.15) and 20 obese (BMI= 34.15± 3.54) . The average plasma levels of C-reactive protein determined in the study was 2.98± 2.58 mg/l and ranged from 0.10 to 13.3 mg/l (Table.1) .

No difference in age was noted between the 3 BMI groups. Geometric mean concentrations of C-reactive protein were increased with increasing BMI categories. The normal weight group had the lowest levels of c-reactive protein(2.15 ±2.52 mg/l) and obese the highest(3.95± 2.78 mg/l) with the overweight being in between(2.87 ± 2.22 mg/l) (Figure.1).

The difference between the normal and overweight was insignificant also between the overweight and obese but the difference in C-reactive protein between the normal and obese group was significant $t(39)= -2.169$, $p<0.05$ and ANOVA was done to determine the difference between the 3 groups and it was insignificant .

TABLE 1. DEMOGRAPHIC AND BIOCHEMICAL CHARACTERISTICS OF THE STUDY POPULATION .

	Normal	Overweight	Obese
Number (M/F)	21(14/7)	20(16/4)	20(11/9)
Mean Age(y)	25.19	30.55	30.75
BMI, kg/m2	22.17±1.45	27.68± 1.15	34.15± 3.54
CRP (mg/L)	2.15 ±2.52	2.87 ± 2.22	3.95± 2.78

Abbreviations: BMI: Body Mass Index , CRP: C-reactive Protein .

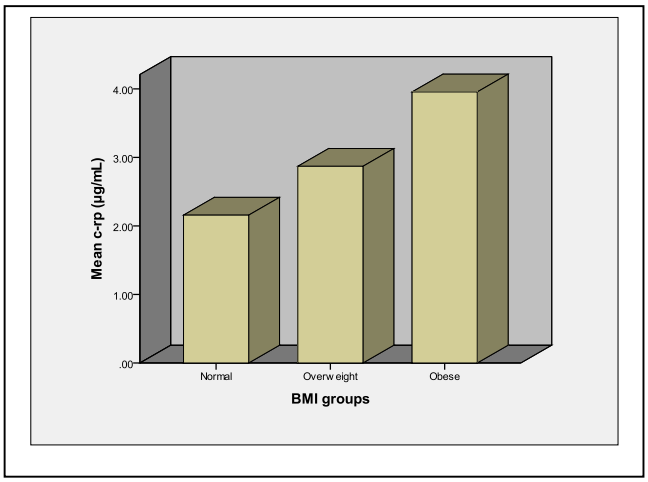

Fig.1. C-reactive protein mean levels in normal, overweight and obese groups .

Plasma levels of C-reactive protein showed a positive and significant correlation with body mass index ($p< 0.05$) and the two variables were plotted in a scatter plot which showed a positive relationship (C-reactive protein is increased with increased BMI) (Figure.2) .

In this present study females had a higher levels of C-reactive protein (4.23± 3.17 mg/l) than males (2.36±2.02 mg/l) and the difference was significant with a $t(59)=-2.79$, $p<0.05$, and this was not due to difference in BMI as the difference between the BMI in males and females was not significant .

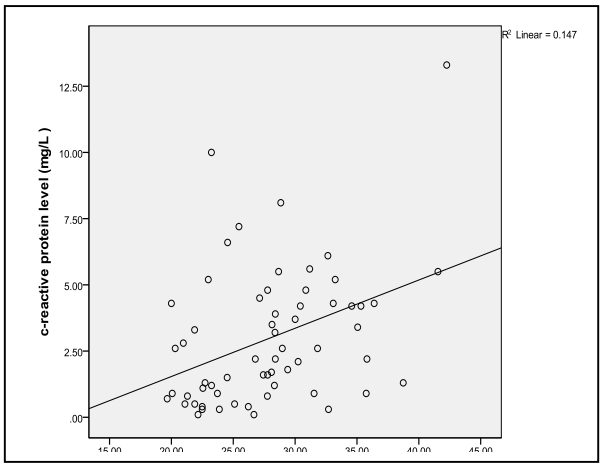

Fig.2. Scatter plot for association between C-reactive protein levels and BMI

The C-reactive protein level was divided in this study according to the American Heart Association into 3 groups with people who had levels of C-reactive protein of less than 1 mg/l defined as (low risk) , between 1 and 3 mg/l (average risk) and more than 3mg/l as(high risk) to have cardiovascular diseases (Table.2) . 17 of the participants were found at low risk , 18 with an average and 26 with high risk .As shown in (Figure .3)and (Table .3), half of the normal weight people were at low risk with the other half divided between average and high risk , and most of the obese were at high risk .

Higher percentage of females were found to be at high risk group as expected as since the females had higher mean of c-reactive levels than males (previously mentioned) (Figure.4).

TABLE 2. CARDIOVASCUALR DISEASE RISK ASSESMENT CATEGORIES ACCORDING TO THE AMERICAN HEART ASSOSCIATION

Cardio CRP value (mg/L)	CVD Risk Level according to AHA/CDC Guidelines
<1.0	Lower relative cardiovascular risk
1.0 - 3.0	Average relative cardiovascular risk
3.1 - 10.0	Higher relative cardiovascular risk. Consider retesting in 1 to 2 weeks to exclude a benign transient elevation in the baseline CRP value secondary to infection or inflammation.
>10.0	Persistent elevation, upon retesting, may be associated with infection and inflammation

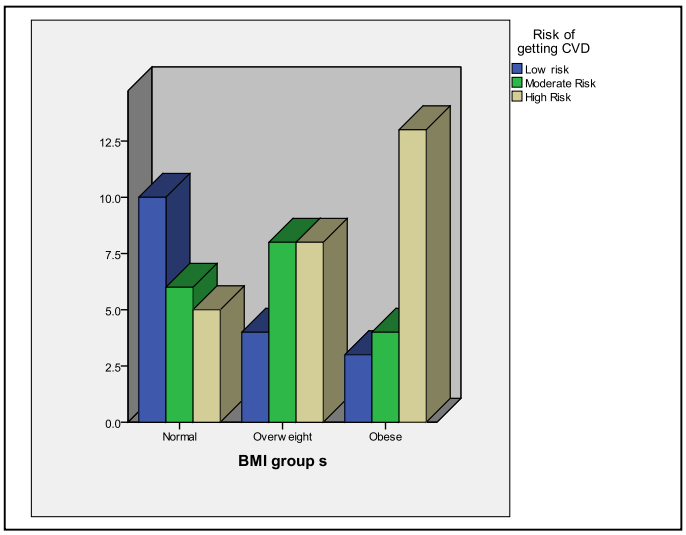

Fig.3. Risk of getting cardiovascular diseases in different BMI groups.

TABLE 3. CROSS-TABULATION BETWEEN BMI GROUPS AND CVD RISK

BMI group	CRP group			Total
	Low risk	Moderate Risk	High Risk	
Normal	10	6	5	21
Overweight	4	8	8	20
Obese	3	4	13	20
Total	17	18	26	61

AAbbreviations: CRP: C-reactive protein, CVD: Cardiovascular diseases, BMI: Body Mass Index

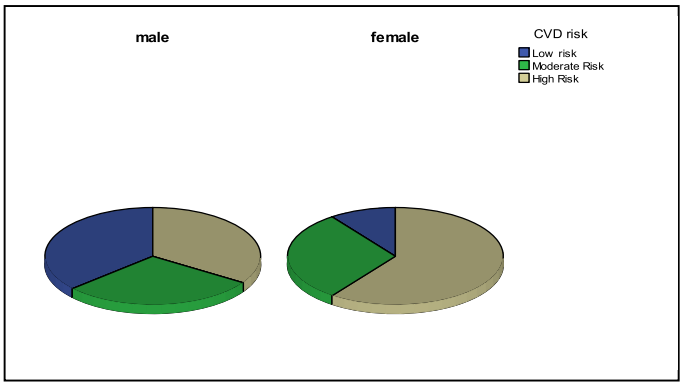

Fig.4. Distribution of CVD risk in males and females

IV. DISCUSSION

In this present study the significant relationship between plasma levels of C-reactive proteins and BMI was consistent with the previous researches. Several mechanisms may link obesity and elevated concentration of C-reactive protein. Expression of tumor necrosis factor (TNF)-a and circulating concentrations of TNF-a are increased in obesity [16] .TNF-a can stimulate the production of C-reactive protein, and promote the production of macrophage migration inhibitory factor , a proinflammatory cytokine. Furthermore, serum concentrations of interleukin (IL)-6, which also promotes the production of C-reactive protein, may be raised in individuals who are obese. C-reactive protein may reflect indirectly the associations between other factors, such as TNF-a or IL6, and BMI.

Other possible reason for the apparent association between C-reactive protein and BMI is that individuals with obesity are at increased risk for various chronic diseases, several of which are also characterized by elevated C-reactive protein concentrations e.g cardiovascular diseases.

Only one published study was done in this concept in Sudan; the study was done on 158 Sudanese adults, the study found that obesity seems to cause dyslipidemia among Sudanese adult males but not females among whom hypertension is a more evident outcome, probably due to increased CRP levels. However, there were no research done to investigate the relation between C -reactive protein and BMI [17].

Limitations of this study must be considered. First, the small sample size. Second, correlation of C-reactive protein with other anthropometric measures as Waist-hip girth ratio, measures of body composition, and body fat distribution would reflect more the relation between C-reactive protein and increased adipose tissue content. Third, maybe there are other conditions that this study was unable to exclude that are associated with elevated C-reactive protein concentration and may have produced the observed results if they tend to occur more frequently among individuals who are obese also subclinical disease may have been responsible for the observed association and it is possible that obesity is accompanied by an inflammatory component unrelated to accompanying clinical or subclinical pathology.

In studies involving large numbers of patients, CRP levels seem to be correlated with levels of heart disease risk. Data from the Physicians Health Study, a clinical trial involving 18,000 apparently healthy doctors, found that elevated levels of CRP were associated with a threefold increase in the risk of heart attack.

According to the American Heart Association CRP is an independent predictor of future cardiovascular events and the AHA recommends measuring CRP levels in patients who - on

the basis of multiple risk factor scoring with cholesterol levels, weight, level of exercise, smoking history, and presence of hypertension and diabetes - appear to have a moderately elevated risk of cardiovascular events. In these patients, an elevated CRP measurement would indicate that the risk may very well be much greater than "moderate." Such knowledge might spur both the doctor and the patient to adopt more aggressive risk-reducing measures.

Three categories have been defined for cardiovascular disease risk assessment (Table.1).

A Cardio CRP level of >3 (up to 10) mg/L may allow for "intensification of medical therapy to further reduce risk and to motivate some patients to improve their lifestyle or comply with medications prescribed to reduce their risk.

Females in this study were found to have a significant difference in c reactive protein level from males and the difference was not due to difference in body mass index. When the AHA and CDC set cutoffs for high and low CRP, it was assumed that levels were similar in men and women. Research now shows that women have higher levels of CRP than men. A Dallas study of nearly 2,750 people aged 30 to 65 years (more than half were women) found that CRP levels were almost twice as high in women than in men (3.3 vs. 1.8 mg/L)[18].

Further research is needed to determine the cause of the difference , whether gender differences in CRP levels contribute to differences in cardiovascular outcomes, and whether thresholds for cardiovascular risk assessment should be adjusted for different gender groups.

V. CONCLUSION

In conclusion, this study has shown that in Sudanese adults a positive and significant relationships between levels of CRP and measures of obesity (BMI) also a relation was found between obesity and risk of developing cardiovascular diseases, These findings suggest a state of low-grade systemic inflammation in overweight and obese persons, the result of this study extend recent observations made by other investigators.

This study recommend a more detailed study of inflammatory cytokines, in relation to obesity, that may reflect the mass and/or activity of the adipose tissue and more researches are needed in Sudan to study the possible therapeutic measures that can be done targeting C-reactive protein aiming for decreasing known complications of cardiovascular diseases.

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