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Original Article

The Circulating markers of inflammation and insulin sensitivity in southern Indian adult subjects: Associations with age, gender and different degree of body mass index.

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ABSTRACT

Abstract:Important biochemical markers for the low-grade inflammation that characterize the earliest events in the pathogenesis of atherosclerosis are CRP and cytokine IL-6. This study aims to evaluate, in healthy Southern Indian adult subjects aged 20–59 years, the association of CRP, IL-6with their age, gender, different degree of body mass and insulin sensitivity.Methods: There were 490 subjects (228 males and 262females) aged 20–59 yrs. All had detailed clinical examination, anthropometry (BMI, WC and WHR) and assessment of fasting Blood glucose, serum levels of CRP, IL-6 and insulin and Insulin resistance by HOMA-IR. Associations with accepted determinants were explored by regression analyses. Results and conclusion: Increase levels of inflammation and insulin resistance were observed in the overweight and obese males of 40 - 59 age group of the south Indian adults.

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1. Introduction

Inflammation is a physiological response of the organism to harmful stimuli, namely Infection or tissue injury. The response provided is usually set towards the reestablishment of homeostasis. It involves the coordinated action of many cell types and mediators, whose involvement depends on the nature of the initial stimulus [1, 2]. The normal acute inflammatory response involves the delivery of plasma components and leucocytes to the site of injury and is initiated by tissue macrophages and mast cells. In response to the above condition, different types of inflammatory mediators are produced (chemokines, cytokines, vasoactive amines, eicosanoids and products of proteolytic cascades) [1, 2]. The coronary artery disease risk factors frequently coexist and share multiple common metabolic pathways [3-5]–. Diabetes, hypertension, and dyslipidemia have all been demonstrated to be associated with inflammation. However, the concept that obesity is characterized by active inflammation is a relatively new concept that initially was not widely accepted. The previous perception of obesity was that adipose tissue simply represented a passive storage depot for excess energy resulting from increased caloric intake relative to energy expenditure [6].

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Adipose tissue was subsequently demonstrated to be a metabolically active endocrine organ. The increase in body mass index was associated in the pathogenesis of diabetes, hypertension, and dyslipidemia. Adipose tissue has shown to be closely involved in a variety of inflammatory processes and the mechanisms have been incompletely described. Adipose tissue is the source of number of cytokines that regulate the production of inflammatory mediators including C-reactive protein, tumor necrosis factor-α, interleukin-6 [7, 8].

Insulin resistance is thought to play a significant role in the pathogenesis of several cardiovascular risk factors in obese subjects [9]. Adipocytes have been implicated as the initial sites of inflammation in obesity and precede the involvement of other organ systems. C-reactive protein has been demonstrated to modify the association of inflammatory cells into adipose tissue via the production of a variety of chemokines particularly IL6.

Monocyte migration and subsequent transformation into macrophages within adipose tissue are key factors in the low-grade inflammation associated with obesity. Oxidative components of modified low-density lipoprotein (LDL) induce a chronic inflammatory processes that implicates the arterial endothelium damage and ultimately results in the complications of CAD [10,11]. Markers of inflammation, such as C-reactive protein have been shown to be associated with an increased risk of CAD in

men and women [12, 13]. Hence the inflammatory processes may also be potential targets of therapy in preventing or treating CAD [14, 15].

Earlier studies have revealed that the plasma concentration of inflammatory mediators, such as C-reactive protein, interleukin-6 and many other molecules levels are increased in the insulin-resistant states of overweight and obesity as compared to normal weight subjects[16-19]. An increase in inflammatory mediators has been shown to predict the future development of obesity and type 2 diabetes [20, 21]. An early recognition of increased circulatory inflammatory mediators has shown to predict the future development of CAD in later life [22-25]. While inflammatory changes in obesity have been recognized for many years, the pathophysiology underlying these alterations is still being elucidated.

The reason for increased production of CRP in obesity is most likely due to IL-6. IL-6 is a cytokine that activates the production of CRP from the liver and CRP levels are a direct indicator of IL-6 levels in vivo [26]. Approximately 25–30% of serum IL-6 originates from adipose tissue and the secretion of IL-6 from subcutaneous fat is in proportion to fat mass [27]. Omental fat cells secrete approximately 2–3 times more IL-6 as compared to subcutaneous adipocytes [28]. Therefore subjects with more abdominal fat may have increased IL-6 and CRP, which could partially account for increased mortality rates in abdominally obese subjects ifIL-6 or CRP contributed to disease promotion.

The present study therefore attempts to evaluatethe association of inflammatory markers with insulin sensitivity in the homogeneous population of healthy living southern Indian adult subjects and explore how these various parameters are influenced by various determinants like body mass index, age, gender.

Methods

To study the association of various cardiovascular risk factors such as circulating inflammatory markers and insulin sensitivity with age, gender and different degree of body mass index in southern Indian adult subjects, we performed simple random sample; cross sectional study in vinayakamission hospital Salem, South India. The study was conducted between the year 2008 and 2010.The participants were recruited from the outpatient clinics who are attending for general health checkup and also student and faculty as volunteers. In the present study a total of 490subjects; male (228) and females (262) of aged 20 – 59 years were included in the present study. Subjects in different age groups were: 20–39 years 223 (110 males and 113 females) and 40–59 years 267 (118 males and 149 females).Informed consent was obtained from all subjects. History of previously diagnosed hypertension, diabetes, anyknown cardiovascular disease or other disease and smoking status or tobacco use was obtained and these subjectswere not included in this study.Height, weight, waist and hip circumferences measurements were recorded using previously reportedmethodology by a singlet trained observer [29]. Blood pressure (BP) was recorded using a standard mercury sphygmomanometer with the subject seated and rested for five minutes. At least two readings at 5 minute interval were recorded and in case of an abnormal reading, another reading was obtained after 30 minutes. The data of anthropometric parameters height, weight, waist size, and hip size and blood pressure measurements were available for all subjects. Height and weight were measured with calibrated instrument. Waist was measured using anon-stretch tape. [29].

Blood sample was collected from an antecubital vein after an overnight fasting. Serum sample was used to measure Fasting glucose, insulin, and lipid parameters immediately. For hs-CRP and IL-6, a venous blood sample was put into tubescontaining trisodiumcitrate (1:9 dilution), Samples were centrifugedwithin 15 min at 3000 rpm for 10 min and the supernatant plasma samples were transferred intoeppendorftubes to be stored at - 80 0 C until analysis. Randox daytona analyzer was used for all biochemical parameters. Serum fasting glucose level was measured by the glucose oxidase method (randox kit).Serum insulin level was measured by chemiluminescent enzyme immunoassay (Abbott Axsym). Insulin sensitivity parameter (HOMA-IR) was derived from the fasting plasma insulin and glucose values using the HOMA model [30].Using thawed plasma sample Quantitative determination of High sensitivity CRP (hsCRP) measurements were performedby solid phase chemiluminescent immunometric assays on the Abbott Axsym analyzerand IL-6 assay was performed by thecommercially available enzyme-linked immunoabsorbent method according to manufacturer's instructions.

Statistical analysis

Approximate normality was assessed for anthropometric and biochemical parameters. SPSS 16 statisticalsoftwarewas used for data analyses. Quantitative characteristics were summarized by arithmetic mean and standard deviation. The differences in the anthropometric and biochemical parameters were compared using t-test. Three Groups based on BMI - mean values of various anthropometric and biochemical characteristics were compared using one way ANOVA followed by post-hoc Bonferroni test. Anthropometric and biochemical characteristics were further categorized according to the cut offvalues. P value < 0.05 was considered statistically significant.

Results:

Data of 490 subjects (males 228, females262) were evaluated in the present study. Subjects in different age groups were: 20–39 years 223 (45.5 %, 110 males and 113 females) and40–59 years 267(54.48%, 118 males and 149 females). Various anthropometric and biochemical characteristicsof the study population are presented in (Table 1.1 & 1.2).

Table 1.1: Various baseline clinical, anthropometric and biochemical characteristicsof different degree of overweight subjects based on body mass index (BMI)

Characteristics	Normal weight (BMI:18.5 – 24.9 kg/m^2) n = 197	Overweight (BMI:25–29.9 kg/m^2) n = 163	Obese (BMI: 30 – 34.9 kg/m^2) n = 130	p
Height (cm)	160.11 ± 12.69	162.35 ± 10.39	158.33 ± 8.34	0.204
Weight (kg)	55.94 ± 10.87	71.02 ± 9.90	80.34 ± 10.08	< 0.001
Body Mass Index (kg/m2)	21.90 ± 1.54	26.55 ± 1.16	32.34 ± 1.29	< 0.001
Waist circumference (cm)	71.09 ± 10.67	88.12 ± 9.76	104.43 ± 7.86	< 0.001
Hip circumference (cm)	90.74 ± 10.29	99.93 ± 11.92	111.63 ± 15.17	< 0.001
Waist to hip ratio	0.768 ± 0.08	0.892 ± 0.09	0.934 ± 0.05	< 0.001
Systolic BP (mm Hg)*	113 ± 13.60	117 ± 12.82	128.49 ± 12.40	< 0.001
Diastolic BP (mm Hg)	79.09 ± 5.85	85.31 ± 7.08	95.08 ± 8.86	< 0.001
Fasting blood glucose (mg/dl)*	82.02 ± 8.91	83.19 ± 12.89	93.24 ± 14.50	< 0.001
Total cholesterol (mg/dl)	144.28 ± 25.67	159.68 ± 24.91	176.58 ± 32.03	< 0.001
LDL cholesterol (mg/dl)	106.96 ± 23.73	125.22 ± 25.30	139.67 ± 28.45	< 0.001
Triglycerides (mg/dl)	103.63 ± 22.89	128.81 ± 27.94	149.60 ± 38.54	< 0.001
HDL cholesterol (mg/dl)**	42.68 ± 8.29	37.15 ± 7.36	33.38 ± 7.61	< 0.001
Total : HDL cholesterol	3.53 ± 1.07	4.49 ± 1.23	5.60 ± 1.90	< 0.001
Insulin (µU/ml)	11.36 ± 1.70	15.16 ± 2.85	24.14 ± 3.78	< 0.001
Insulin resistant (HOMA- IR)	2.05 ± 0.36	3.54 ± 0.78	5.42 ± 1.69	< 0.001

Values are expressed as mean ± SD; Statistical significance by ANOVA followed by post-hoc Bonferroni test;
*No significance between normal and overweight; ** No significance between overweight and obese

Table 1.2: Various baseline characters of adipokines, inflammatory markers of different degree of overweight subjects

Characteristics	Normal weight (BMI:18.5 – 24.9 kg/m^2) n = 197	Overweight (BMI:25–29.9 kg/m^2) n = 163	Obese (BMI: 30 – 34.9 kg/m^2) n = 130	p
hs-CRP (mg/dl)	0.64 ± 0.23	0.98 ± 0.42	1.93 ± 0.58	< 0.001
IL-6(pg/dl)	1.46 ± 0.4	2.45 ± 0.9	3.73 ± 1.3	< 0.001

Values are expressed as mean ± SD; Statistical significance by ANOVA followed by post-hoc Bonferroni test

The average Fasting Blood Sugar (FBS) of the subjects in the study is varied from 81 to 98 mg/dl. The maximum FBS is observed in the age group of 40 to 60 years male and the minimum in 20-39 years female. The maximum FBS isobserved in the obese subjects and minimum in the normal subjects. The average FBS is comparatively higher in male than female subjects.

The average insulin of the subjects in the study is varied from 10.9 to 27.4 µU/ml. The maximum insulin is observed in the age group of 40 to 60 years male and the minimum in 20-39 years female. The maximum insulin level isobserved in the obese subjects and minimum in the normal subjects. The average insulin level is comparatively higher in male than female subjects. Insulin is positively correlated with the parametersstudied such as BMI, hs-CRP and IL-6. It is also positively but not significantly correlated with FBS.

The average Insulin resistance (IR) of the subjects in the study is varied from 1.81 to 4.91. The maximum IR is observed in the age group of 40 to 60 years male and the minimum in 20-39 years female. The maximum IR isobserved in the obese subjects and minimum in the normal subjects. The average IR is comparatively higher in male than female subjects. IR is positively correlated with the parametersstudied such as BMI, hs-CRP and IL-6.

The average hs-CRP levels of the subjects in the study are varied from 0.32 to2.38mg/dl. The maximum hs-CRP level is observed in the age group of 40 to 60 years female and theminimum in 20-39 years male. The maximum hs-CRP levels are observed in the obese subjects and minimum in the normal subjects. The average hs-CRP level is comparatively higher in female than male subjects. hs-CRP levels is positively correlated with the parameters studied such as BMI, insulin, insulin resistance, and IL-6.

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The average IL-6 of the subjects in the study is varied from 1.18 to 3.90 pg/ml. The maximum IL-6 is observed in the age group of 40 to 60 years female and the minimum in 20-39 years female. The maximum IL-6 is observed in the obese subjects and minimum in the normal subjects. The average IL-6 is comparatively higher in male than female subjects. IL-6is positively correlated with the parameters studied such as BMI, insulin, insulin resistance and hs-CRP.

Table 1.3: Spearman's correlation coefficients and associated p-values relationships of various anthropometric, metabolic characters and inflammatory status with different obesity index

Variables		Body mass index	Waist circumference	Waist to hip ratio
Body mass index	r	1.000	0.83	0.72
	p	-	< 0.01	< 0.01
Waist circumference	r	0.83	1.000	0.64
	p	< 0.01	-	< 0.01
Waist to hip ratio	r	0.72	0.64	1.000
	p	< 0.01	< 0.01	-
Fasting glucose	r	0.29	0.29	0.27
	p	< 0.01	< 0.01	< 0.01
Insulin	r	0.85	0.77	0.66
	p	< 0.01	< 0.01	< 0.01
Insulin resistant	r	0.85	0.78	0.62
	p	< 0.01	< 0.01	< 0.01
hs-CRP	r	0.71	0.59	0.51
	p	< 0.01	< 0.01	< 0.01
IL – 6	r	0.61	0.51	0.49
	p	< 0.01	< 0.01	< 0.01

Discussion

The major cardiovascular risk factors often coexist and share multiple common metabolic pathways. It was earlier thought that adipose tissue simply represented a passive storage depot for excess energy resulting from increased caloric intake relative to energy expenditure. The previous perception of obesity was that adipose tissue was subsequently demonstrated to be a metabolically active endocrine organ and the subsequent increase in body mass index (BMI) was implicated in the pathogenesis of diabetes, hypertension, and dyslipidemia. The present study revealed that the Fasting blood glucose,Insulin level and Insulin resistance (HOMA-IR)was positively correlated with BMI. The prevalence of high insulin resistance among the male obese subjects was observed than the female obese subjects. The prevalence of insulin resistance in the age group of 20-39 years overweight and obese subjects was lower than the age group of 40-59 overweight and obese subjects in this study.

Spearman correlation coefficient was used to find the relationships and strength of association between each of independent parameter with BMI. Fasting blood glucose was positively correlated with BMI (r= 0.29). Insulin level was positively correlated with BMI (r= 0.85) and Insulin resistance (HOMA-IR) was positively correlated with BMI (r= 0.85)(Table 1.3).

Fasting blood glucose of males and females was positively correlated with BMI (r= 0.36; r= 0.22) respectively(Table 1.4). Insulin level in males and females was positively correlated with BMI (r= 0.84; r= 0.64) and Insulin resistance (HOMA-IR) was positively correlated with BMI (r= 0.89; r= 0.75) respectively (Table 1.4).

Fasting blood glucose of Age 20-39 years and age 40-59 years subjects was positively correlated with BMI (r= 0.34; r= 0.25) . Insulin level was positively correlated with BMI (r= 0.83; r= 0.84) and Insulin resistance (HOMA-IR) was positively correlated with BMI (r= 0.74; r= 0.89) respectively (Table 1.5).

Adipose tissue has been shown to be strictly involved in a variety of inflammatory processes and the mechanisms have been incompletely understood. Obesity was recently thought to be characterized by dynamic inflammation. Recent findings suggest that the adipose tissue is the source of a number of cytokines that regulate the production of inflammatory mediators including C-reactive protein, interleukin-6.

Inflammatory changes in obesity have been recognized for many years. Similar to the present study, several earlier studies have demonstrated increased plasma concentration of

inflammatory mediators such as CRP and IL-6 in obese subjects [31, 32]. Earlier studies also have confirmed that CRP levels are increased in overweight and obese subjects [33, 34]. Increased levels ofinflammatory marker, C-reactive protein (CRP) [35, 36], have been associated with an increased risk of CVD, and thus inflammatory processes may also be a potential target for the therapy in preventing or treating CVD [37, 38]. Hence in the present study the inflammatory markers:hs-CRP and IL-6 were studied in overweight and obese subjects.

In the present study, a significant increase levels of hs-CRP and IL-6 were observed in the overweight and obese subjects as compared to normal subjects, higher level was seen in males as compared to females and it was higher in 40 - 59 age group as compared to 20 - 39 age group. Adipose tissues are the important source of the high circulating hs-CRP and IL-6 found in obese individuals [39, 40] and closely related to the amount of total body fat mass [31]. The CRP levels in healthy normal weight adults were significantly lower than those found in overweight or obese subjects [41, 42]. Several studies have reported higher CRP and IL-6 levels among men and women with increasing BMI [43, 44]. Previousstudies have proven that weight loss in obese shown to affect a decrease in CRP levels [45, 46].

Spearman correlation coefficient was used to find the relationships and strength of association between each of independent parameter with BMI. It was observed that the hs-CRP level was positively correlated with BMI (r= 0.71) and IL-6 level was also positively correlated with BMI (r= 0.61) (Table 1.3)

hs-CRP level of males and females was positively correlated with BMI (r= 0.73; r= 0.70) and IL-6 level of males and females was positively correlated with BMI (r= 0.63; r= 0.59) respectively (Table 1.4).hs-CRP level of Age 20-39 years and age 40-59 years subjects were positively correlated with BMI (r= 0.55; r= 0.75) and IL-6 level of Age 20-39 years and age 40-59 years subjects were positively correlated with BMI (r= 0.61;r= 0.54) respectively (Table 1.5).

Thus it can be concluded that an increase level of inflammation and insulin resistance were observed in the overweight and obese males of 40 - 59 age group of the south Indian adults as compared to other group that are studied.

Table 1.4: Spearman's correlation coefficients and associated p-values relationships of various metabolic characters and inflammatorywith BMI at Gender wise

Variables		*MALE BMI*	*FEMAL EBMI*
FBS	r	*0.369*	*0.224*
	p	*<0.01*	*<0.01*
Insulin	r	*0.840*	*0.859*
	P	*<0.01*	*<0.01*
Insulin resistant	r	*<0.01*	*<0.01*
	p	*<0.01*	*<0.01*
hs-CRP	P	*0.703*	*0.713*
	r	*<0.01*	*<0.01*
IL-6	p	*0.597*	*0.631*
	r	*<0.01*	*<0.01*

Table 1.5: Spearman's correlation coefficients and associated p-values relationships of various metabolic characters and inflammatory status with BMI at Agewise

Variables		Age 40 – 59 years BMI	Age 40 – 59 years BMI
FBS	r	0.336	0.249
	p	<0.01	<0.01
Insulin	r	0.836	0.840
	P	<0.01	<0.01
Insulin resistant	r	0.743	0.888
	p	<0.01	<0.01
hs-CRP	r	0.554	0.755
	p	<0.01	<0.01
IL-6	r	0.611	0.544
	p	<0.01	<0.01

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