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Molecular and Biochemical Studies on Subjects with Increased Waist Circumference

KEYWORDS: Waist circumference, Cardiovascular disease, Cytokinesis-block micronuclei assay, Oxidative Stress and Malondialdehyde

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ABSTRACT *Waist circumference (WC) is a simple measurement to indicate the need for weight management and is a convenient way of measuring abdominal or central obesity. WC appears to increase the risk of obesity related complications and several chronic illnesses including cardiovascular disease (CVD) and excess mortality. Overweight and obesity have been increasing within the UK population over the past 15 years among both adults and children. This trend is also being observed in other countries. Goal of the present study was to find out the effect of molecular and biochemical studies on subjects with increased waist circumference. The present study consists of 45 study subjects and 25 healthy subjects without any chronic illness were selected as control for this study. Detailed demographic, clinical and lifestyle characteristics were compared with subjects. The role of oxidative stress was measured by Malondialdehyde (MDA) and the DNA damages were quantified by Cytokinesis-Block Micronuclei (CBMN) assay. The mean MDA value and the micronuclei frequency was significantly elevated in study subjects as compared with that of control subjects. Abdominal fat is closely involved in the production of oxidative stress. This suggests that molecular and biochemical effects may be one of the important causes for abnormal abdominal fat with increased waist circumference.*

INTRODUCTION

Waist circumference was defined as the average of two measurements taken after subjects inspiration and after expiration (mean difference between the two measurements approximately 1.5 cm) at the midpoint between the lowest rib and iliac crest (Lakka et al., 2000). Waist circumference (WC) and waist to hip ratio (WHR) are the most common proxy measures of visceral adipose tissue (VAT). Both measures are correlated with VAT; however, WC is more strongly associated with VAT (Onat et al., 2004). Despite this, WHR may be a better predictor of CVD risk as hip circumference is inversely associated with the development of cardio metabolic risk factors and cardiovascular disease (CVD) (Lissner et al., 2001; Seidell et al., 2001; Okura et al., 2004; Heitmann et al., 2004). In the adult population, waist circumference measurement has proved to be a useful tool for assessing risk for obesity related diseases such as CVD (Lemieux et al., 2000).

Obesity is a global public health crisis and potent risk factor for metabolic disease and CVD at the population level (Kim, 2007; Faloia, 2009). Abdominal fat deposition is a key component of obesity (Sharma, 2002). Abdominal obesity is increasingly recognized as a major risk factor for CVD. Compared with body mass index (BMI), anthropometric measures of abdominal obesity appear to be more strongly associated with metabolic risk factors (Wang et al., 2005; Despres et al., 2006). According to the International Diabetic Federation (IDF) definition, metabolic syndrome is present if a man has a waist circumference ≥94 cm in addition to two or more the conditions such as high triglyceride level, low HDL cholesterol level, elevated blood pressure, and elevated glucose value (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). WHR has been suggested to be a superior predictor of CVD risk because it includes a measurement of hip circumference, which is inversely associated with dysglycaemia, dyslipidaemia, diabetes, hypertension, CVD and death (Lissner et al., 2001; Seidell et al., 2001; Okura et al., 2004; Heitmann et al., 2004). Epidemiological data showed increase in incidence and prevalence of diseases associated with endocrine disrupting chemicals such as breast, prostate, and testis cancer, diabetes, obesity, and decreased fertility over the last 50 years (Curado et al., 2007).

In men, a reduction in free testosterone level is inversely associated with obesity (Derby et al., 2006). Menopause is also associated with an increase in fat mass and a redistribution of fat to the abdominal area (Toth et al., 2000). Wells et al., (2009) found that changes in waist and hip circumferences correlated directly with changes in weight, but there were differences in the pattern of change by sex. On average, with a 4.5 kg weight gain, men had a 4 cm

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increase in WC and a 2.5 cm increase in hip circumference. Comparable values for women were 3.3 cm and 3.6 cm respectively.

Etiological factors of obesity include the binge eating disorder, high glycemic diet, sedentary lifestyle and use of certain medications like psychotropic drugs (Martınez, 2002). Other etiological factors have been proposed in the pathogenesis of obesity-induced insulin resistance. These factors include oxidative stress, mitochondrial dysfunction, intracellular lipid accumulation in skeletal muscle and liver and decreased β-oxidation (Aguirre et al., 2000; Saltiel and Kahn, 2001; Emanuelli et al., 2001; Hundal et al., 2002; Trayhurn, 2005; Yasukawa et al., 2005; Houstis et al., 2006; Schattenberg et al., 2006; Bagry et al., 2008).

Reductions in waist circumference should be a primary aim of strategies designed to reduce health risks associated with metabolic syndrome. Exercise is associated with substantial reductions in waist circumference (Ross et al., 2000; Donnelly et al., 2003; Ross et al., 2004) and that cardiorespiratory fitness significantly attenuates the mortality risk associated with metabolic syndrome (Katzmarzyk et al., 2004). Previous studies have shown that using a lower waist circumference threshold within the context of metabolic syndrome increases the prevalence, but decreases the risk of mortality (Lakka et al., 2002) and type 2 diabetes (Laaksonen et al., 2002).

C-reactive protein (CRP) concentrations have been shown to be directly related with malondialdehyde (MDA)-modified LDL concentrations (Hulthe et al., 2001). The elevated CRP concentrations were related to increased abdominal fat (Barinas et al., 2001; Hulthe et al., 2001). Leptin modulates key processes involved in atherogenesis, including angiogenesis, oxidative stress, vascular calcification and thrombosis suggest a role for leptin as a potential cardiovascular risk factor in obese and diabetic patients (Yamagishi et al., 2001; Parhami et al., 2001).

Oxidative DNA damage might also play an important role in the process of carcinogenesis (Valko et al., 2006). The relation between body size and incidence of prostate cancer is complex (MacInnis et al., 2006; Giovannucci et al., 2007; Ma et al., 2008; Robinson et al., 2008; Discacciati et al., 2011; Cao et al., 2011). At high concentration, reactive oxygen species were important mediators to the damage of cell structures, nucleic acids, lipids and proteins (Valko et al., 2006). Due to this, consumption of fruits and vegetables containing a mixture of natural antioxidant and phytochemical compounds are linked to the protection of biological system from the oxidative DNA damage and further reduced prostate cancer risk.

Drugs approved by the Food and Drug Administration (FDA) for the long term management of obesity, including weight loss and maintenance of weight loss are used in conjunction with a reduced calorie diet and are recommended for patients with an initial body mass index (BMI) ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors (e.g., type2 diabetes (T2D), dyslipidemia, controlled hypertension). Current strategies for the treatment of obesity include lifestyle interventions, pharmacotherapy and bariatric surgery. Although dietary treatment associated with exercise is the cornerstone of treatment, it is very often inadequate. Bariatric surgery reduces the size of the stomach, increases the feeling of fullness, and reduces the amount of food intake (Demaria et al., 2007).

Increase in waist circumference is the major criteria to identify metabolic syndrome. Therefore the purpose of the present study was to compare the effect of increased waist circumference and CVD risks. Public should be aware about their health status, dieting and exercise which may helps to reduce the size of the waist. No serious attempts were made earlier to correlate between molecular and biochemical studies on subjects with increased waist circumference. Hence the present study was undertaken to aware the people about molecular and biochemical effects on increased waist circumference.

Materials and Methods

Forty five individuals with increased waist circumference were selected for this study. The samples were referred from various centers of Kerala to Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala. Twenty five healthy subjects without any chronic illness were selected as control for this study. Detailed demographic, clinical and lifestyle characteristics were recorded using proforma. In the present study, Cytokinesis Block Micronuclei (CBMN) assay was performed on each sample by using cytochalasin B for quantitating the extent of somatic DNA damages and MDA test was performed for detecting the oxidative stress.

Collected seven ml of blood sample by venepuncture and transferred 3 ml of blood to sodium heparinized vacuutainers for quantifying the extent of somatic DNA damages by cytokinesis-block micronuclei (CBMN) assay. The remaining five ml of blood was transferred into a plain tube. Blood was allowed to clot, serum separated immediately. Blood sugar and lipid profile were estimated using semi-automated clinical chemistry analyzer. The level of the serum lipid peroxide marker, MDA was determined using thiobarbituric acid as main reagent and measuring the values on photoelectric colorimeter at 540nm.

Two ml blood was added to a culture tube containing 10 mL RPMI 1640 supplemented with 100units/mL penicillin, 100µg/mL streptomycin, 15% fetal bovine serum and 100µg/mL phytohemagglutinin. Cytochalasin B was added to the cultures at a final concentration of 4.5µg/mL (Sigma) after 44th hours of initiation of cells with phytohaemagglutinin. Cells were harvested after 72 hr incubation, and they were treated with a hypotonic solution (0.075M KCl) for 1 min and fixed in fresh fixative solution (methanol: acetic acid, 3:1). The cells were dropped onto slides and the slides were air dried and stained with 10% Giemsa. Micronucleated cells were analyzed under light microscopy at 100X magnification. The number of micronuclei is not less than 1000 binucleated cells were scored and the distribution of micronuclei among binucleated cells was recorded.

RESULTS

Forty five individuals with increased waist circumference and twenty five normal healthy individuals were selected and analysed for the present study. Various demographic, clinical, and lifestyle characteristics were recorded and correlated with the extent of oxidative stress and DNA damage. The Cytokinesis block micronuclei assay revealed that the mean CBMN frequency was statistically higher among the study subjects (13.5) than the healthy control subjects (10.47). The MDA value for study subjects was 1.79 whereas in control subject was 1.24. Thus the MDA test in the present study showed a statistically significant difference.

The subjects were grouped on their demographic characteristics such as age, sex, birth order, BMI, residence

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and waist circumference. Among the 45 study subjects, 8 subjects (17.7%) were belonged to age between 24 to 45 years and showed a mean CBMN frequency of 12.51. 31 subjects (68.8%) with age between 46 to 67 years and showed a mean CBMN frequency of 13.76. 6 subjects (13.33%) were belonged to age between 68 to 79 years and showed a mean CBMN frequency of 14.05. The highest mean MDA value (2.01) was showed 68 to 79 years of age group. The mean CBMN frequency (13.66) of female subjects was comparatively higher than male subjects (13.49) and highest mean MDA value (1.81) was showed by female subjects. The birth order ranged from 1 to 12 and majority of the subjects were belonged to <6 birth order (n=38). The highest mean CBMN frequency (13.91) and highest MDA value (1.88) were showed by subjects with >6 birth order. On the basis of BMI, <25 Kg/m^2 showed mean CBMN frequency of 13.5 and >25 Kg/m^2 showed mean CBMN frequency of 13.61. Highest mean CBMN frequency and mean MDA value showed by subjects with BMI of >25 Kg/m^2. The mean MDA value of subjects belonged to sedentary and non-sedentary lifestyle characters were 1.73 and 1.9 respectively. The highest mean CBMN frequency (13.59) and mean MDA value (1.73) was observed in subjects having sedentary lifestyle. Majority of the study subjects were belonged to urban area (77.7%) followed by rural area (22.2%). The highest mean CBMN frequency (13.76) and MDA value (1.84) was observed in urban area. According to waist circumferences, 40 (88.8%) subjects were belongs to the group of 90 to 110 cm waist circumferences with a mean CBMN frequency of 13.48 and mean MDA value of 1.78. 5 (11.11%) subjects were belonged to the group of 111 to 131 cm waist circumferences were showed a mean CBMN frequency of 14.32 and mean MDA value of 1.9. The highest mean CBMN frequency (13.48) and mean MDA value (1.9) were belonged to the group of 111 to 131 cm waist circumferences.

Table 1: Distribution of mean MDA value and mean CBMN frequency according to demographic characteristics of the study subjects

Category	Variables	Total	Percentage (%)	Mean MDA Value	Mean CBMN frequency
Age (Years)	24-45	8	17.7%	1.22	12.51
	46-67	31	68.8%	1.89	13.76
	68-79	6	13.33%	2.01	14.05
Sex	Male	23	51%	1.17	13.49
	Female	22	48.8%	1.81	13.66
Birth order	≤6	38	84.4%	1.77	13.51
	>6	7	15.5%	1.88	13.91
Occupation	Sedentary	33	73.33%	1.73	13.59
	Non-sedentary	12	26.6%	1.9	13.47
Residence	Rural	10	22.2%	1.61	12.93
	Urban	35	77.7%	1.84	13.76

Table 2: Distribution of mean MDA value and mean CBMN frequency according to clinical characteristics of the study subjects

Category	Variables	Total	Percentage (%)	Mean MDA value	Mean CBMN frequency
Random Blood Sugar (mg/dL)	<140	5	11.1%	1.72	13.51
	≥140	40	88.8%	2.31	14.08
Total Cholesterol (mg/dL)	<200	33	73.3%	1.7	13.5
	≥200	12	26.6%	2.03	13.78
Triglyceride (mg/dL)	<150	25	55.5%	1.732	13.5
	≥150	20	44.4%	1.87	13.66
H/o Thyroid disorder	Yes	8	17.7%	1.97	13.92
	No	37	82.8%	1.78	13.5
H/o Diabetes	Yes	18	40%	1.92	14.12
	No	27	60%	1.7	13.21
H/o Hypertension	Yes	14	31.1%	1.75	13.34
	No	31	68.8%	1.89	14.08
H/o CAD	Yes	18	40%	1.86	13.91
	No	27	60%	1.74	13.35
H/o Chronic illness	Yes	37	82.2%	1.9	13.51
	No	8	17.7%	1.77	13
H/o Renal failure	Yes	3	6.66%	2.1	14.53
	No	42	93.3%	1.77	13.5
H/o Infertility	Yes	5	11.11	1.99	14.34
	No	40	88.8	1.76	13.48

Table 3: Distribution of mean MDA value and mean CBMN frequency according to lifestyle characteristics of the study subjects

Category	Variables	Total	Percentage (%)	Mean MDA value	Mean CBMN frequency
BMI (kg/m^2)	<25	16	35.5%	1.68	13.5
	≥25	29	64.4%	1.98	13.61
Waist Circumference (cm)	90-110	40	88.8%	1.78	13.48
	111-131	5	11.11%	1.9	14.32
Smoking	No	9	20%	1.81	13.46
	Yes	36	80%	1.72	13.6
Alcoholism	No	6	86.6%	1.81	13.48
	Yes	39	13.3%	1.65	13.59
Regular exercise	No	30	66.6%	1.79	13.64
	Yes	15	33.3%	1.78	13.45
Physical activity	Good	4	13.33%	2.52	13.4
	Average	35	77.7%	1.73	13.51
	Poor	6	8.88%	1.66	14.37

The subjects were grouped on their clinical and lifestyle characteristics (Table 2 & Table 3). Subjects with random blood sugar level <140 mg/dL showed a mean CBMN frequency of 13.51. Subjects with RBS level >140 mg/dL showed a mean CBMN frequency of 14.08 with mean MDA value of 2.31. Normal serum total cholesterol was reported only in 33 (73.3%) study subjects and the remaining 12 subjects were hypercholesterolemia (>200 mg/dL). The mean CBMN frequency of hypercholesterolemic sub-

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jects were 13.78 and mean MDA value of 2.03. The study subjects showed triglyceride level >150 mg/dL had higher mean CBMN frequency (13.66) and higher MDA value of 1.87 compared to subjects with triglyceride level <150 mg/dL.

The mean CBMN frequency and MDA value based on H/o thyroid disorder were analyzed among the study subjects. Study subjects with H/o thyroid disorder were showed a mean CBMN frequency of 13.92 and the subjects without H/o thyroid disorder was showed a mean CBMN frequency of 13.5. Study subjects with H/o thyroid disorder were showed a mean MDA value of 1.97 and the subjects without H/o thyroid disorder was showed a mean MDA value of 1.78. Subjects with H/o diabetes showed a mean CBMN frequency of 14.12 and mean MDA value of 1.92. This indicates that H/o thyroid disorder and H/o diabetes have correlation with mean CBMN frequency and mean MDA value. Among the 45 study subjects, 14 (31.1%) subjects had H/o hypertension and the mean CBMN frequency was 13.34. The remaining subjects showed no H/o hypertension and mean CBMN frequency of 14.08. Subjects were belonged to H/o hypertension showed a mean MDA value of 1.75. The study evaluate that the mean CBMN frequency level and mean MDA level were higher with those who have H/o CAD and H/o chronic illness with mean CBMN frequency of 13.91 and 13.51. The mean CBMN frequency was studied according to the H/o renal failure. 42 (93.3%) subjects showed no H/o renal failure and the mean CBMN frequency was 13.5. The remaining subjects showed H/o renal failure and mean CBMN frequency was 14.53. Highest mean MDA value (2.1) was observed in subjects belonged to H/o renal failure. Subjects with H/o infertility showed a mean CBMN frequency of 14.34 and mean MDA value of 1.99.

This study indicates that, the subjects with smoking habits have increased mean CBMN frequency (13.6) and mean MDA values (1.72) were compared to nonsmokers. The alcoholism was observed in 39 (13.3%) subjects with a mean CBMN frequency was 13.59. The study subjects without alcoholism (86.6%) showed a mean CBMN frequency of 13.48. Subjects who don't do regular exercise and physical activity were showed the highest mean CBMN frequency.

DISCUSSION

According to WHO (2003), increase in waist circumference is one of the important marker for metabolic syndrome. Obesity is one of the important factors which may leads to produce increase in the waist size. In the present study, subjects with increased waist circumference showed an increase in mean CBMN frequency (13.5) and MDA value than the control subjects (10.47).

International Diabetes Federation (IDF), (2006) reported that increasing prevalence of abdominal obesity defined by using ethnic-specific cut-off values for WC. Age and sex are also related with increase in waist circumference. The present study also suggests that the incidence of waist circumference is increased with increase in age and is higher in females than males. Based on BMI, greater than or equal to 25 is overweight and BMI greater than or equal to 30 is obesity (WHO, 2003). The present study revealed that individuals with increased waist circumference (111 to 131 cm) had a highest mean CBMN frequency (13.61).

In the present study the incidence of waist circumference was observed, people who lived in urban area have higher mean CBMN frequency than rural area. The National Family Health Survey-3 (NFHS-3, 2007) reported that in India, obesity (BMI $\geq$ 25 kg/m^2) was more prevalent in the urban areas and in higher socio-economic groups compared to the rural areas.

Ko et al., (2007) propose the creation of an intermediate state of high WC, the "central preobesity" for Chinese men with WC of 84–90 cm and women with WC of 74–80 cm and waist circumference >102cm in men and >88cm in women may considered as abnormal waist circumference. In the present study, people who have increased waist circumference were showed high risk for obesity and these people also have high mean CBMN frequency (14.32).

Both BMI and waist circumference were significantly higher in men and women with abnormal glucose tolerance. People with undetected diabetes had a higher risk of being obese or having central obesity (Rathmann, 2003). In this present study, about 40% of study subjects have H/o diabetes and also these persons showed high mean CBMN frequency (14.12).

In the present study, individuals with H/o hypertension and without H/o hypertension were found to have a mean CBMN frequency of 14.08 and 13.34. Subjects with H/o hypertension showed increased mean CBMN frequency than the subjects without H/o hypertension. Stevens, (2003) reported that studies in a representative sample of the adult Chinese population that prospectively relate the BMI and waist circumference cutoff suggested to the incidence of hypertension, dyslipidemia, diabetes, clinical cardiovascular disease events, cardiovascular disease mortality, and all cause mortality.

Barter and Rye, (2006) proportionate increase in the WHR (waist to hip ratio) was observed in association with the elevated triglyceride (TG) levels. In the present study TG elevation showed an increase in waist circumference and also increased mean CBMN frequency of 13.66. The present study also suggests that the incidence of waist circumference is associated with smoking and have increased mean CBMN frequency (13.6) than the non smokers. Kuk et al., (2006) reported that a positive association between waist circumference and mortality was found in persons with and without prevalent disease, in smokers and nonsmokers, and in different racial/ethnic groups.

Koh-Banerjee et al., (2003) reported that the studies that have examined the effects of change in diet and physical activity on weight or waist change have found both to be significant independent factors. In the present study, people who do poor physical activity showed an increased waist circumference and also have high mean CBMN frequency (14.37).

Moderate-to-high consumption of alcohol was associated with later high waist circumference, whereas moderate-to-high wine consumption may have the opposite effect (Vadstrup et al., 2003). The present study revealed that in alcoholism the incidence of waist circumferences and mean CBMN frequency was high.

CONCLUSION

The present study involves molecular and biochemical studies on subjects with increased waist circumference. Overweight and adverse fat distribution was associated with increasing waist circumference. The demographic characters such as age, birth order clinical characteristics include diabetes, hypertension, H/o infertility and with

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poor lifestyle factors such as physical inactivity, alcohol consumption and smoking habit, all of these leads to risk for increased waist circumference with high mean CBMN frequency and MDA value. This study suggested that increased physical activity and improved diet will help to reduce increased waist circumference and have a health benefit independent of weight loss. Each lifestyle factor influences the size of waist and the hips differently and understanding these influences was important for health promotion. Thus lifestyle modifications such as smoking cessation and a more physically active lifestyle should all be encouraged, leading to an overall healthier body shape.

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