Effect of Obesity on Antioxidant enzymes and Type 2 Diabetes Mellitus

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Abstract

Obesity refers to body mass index (BMI) greater than 30kg/m^2. The present study aims to assess firstly, obesity as an independent risk factor for decreased activity of antioxidant enzymes in humans and secondly, its role in complicating glucose and lipid metabolism in type 2 diabetic subjects.

The study was conducted on two groups; Group 1 had 50 obese subjects with two subgroups: (a) including 25 type 2 diabetic subjects and (b) 25 obese with different grades of obesity (30-50 kg/m^2) with no history of type 2 diabetes, hypertension, and hyperlipidemia. Group 2 included 25 non-obese type 2 diabetic subjects. Results were compared with 25 age matched healthy controls. Parameters assessed were BMI (weight in kg/height^2 in metres), lipid profile, erythrocyte Superoxide dismutase (SOD) and

Glutathione peroxidase (GPX). They were assessed spectrophotometrically using appropriate kits.

The subjects with healthy BMI had significantly higher ($p<0.001$) erythrocyte SOD (1443.45 ± 176.84 units/gHb) and GPX (95.1 ± 3.6 units/g Hb) than those with BMI above 40kg/m2 (986.0 ± 25.0 units/gHb) and (80.8 ± 7.2 units/gHb). The values (in mg/dl) of cholesterol (C) 276.03 ± 4.62, triglycerides (TG) 186.6 ± 4.02, high density lipoprotein-C (HDL-C) 30.98 ± 0.92,very low density lipoprotein-C (VLDL-C) 37.3 ± 0.76 and low density lipoprotein–C (LDL-C) 207.75 ± 9.23 respectively were significantly higher ($p<0.001$) in subgroup (a) compared to group2 (231.0 ± 8.43, 160.0 ± 5.53, 33.94 ± 1.37, 31.69 ± 1.09, 165.29 ± 6.69). TC, TG, VLDL, HDL-C and LDL-C showed a significantly increasing pattern with increase in BMI. Plasma glucose both fasting and post prandial levels (in mg/dl) showed a highly significant pattern ($p<0.001$) in subgroup (a) (151.7 ± 21.8, 223.03 ± 5.09) compared to group 2(130.34 ± 3.59, 158.2 ± 8.9). FPG and 2hr PG values in obese non diabetic subjects with BMI 40-44 Kg/ m^2,45-50 Kg/m^2 showed significantly higher values compared to subjects with BMI 30-34 Kg/ m^2 [FPG:0.03, 0.001 ;2hrPG: 0.08(not quite significant),0.0005].

It is concluded from the results that obesity independent of additional factors such as hypertension, diabetes mellitus, hyperlipidemia and smoking causes decreased activity of antioxidant enzymes. It should receive the similar attention as obesity with complications. Also, with obesity insulin resistance worsens and the dyslipidemia in type 2 diabetics impairs further.

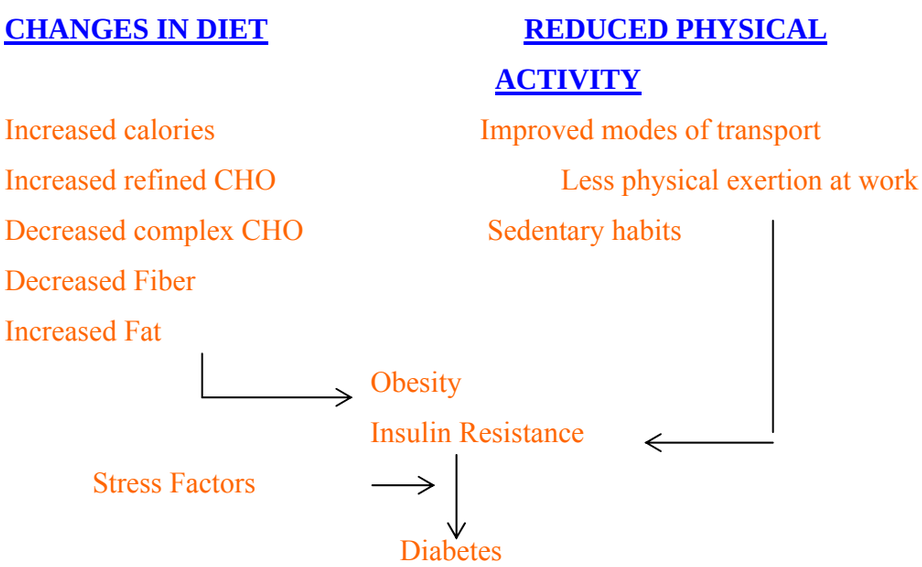
Introduction

Obesity is a condition in which the natural energy reserve stored in the fatty tissue of humans is increased to a point where it is associated with certain health conditions.

Although obesity is an individual clinical condition, it is increasingly viewed as a serious and growing public health problem. Excessive body weight has been shown to predispose to various diseases particularly cardiovascular diseases, diabetes mellitus type 2, sleep apnea and osteoarthritis[1].

The degree of overweight can be expressed in several ways, but the most useful is body mass index (BMI). This index is the body weight in Kgs divided by square of the height in metres (W/H^2). Healthy weight is defined as a BMI between 19 and 25 kg/m^2. Overweight is a BMI of 25-30 kg/m^2 and is associated with low risk. A BMI greater than 30 kg/m^2 is almost always associated with increased mortality and various diseases[2, 3].

The cutoff value for healthy BMI in Indians is below 23 kg/m^2. Despite having lean BMI an adult Indian has more chances of having abdominal obesity. The national Indian survey showed that upper body adiposity was more common (50.3%) than overweight[4, 5]. The new generation of children and adolescents show unprecedented levels of obesity. This foretells not only an epidemic of obesity to be tackled. But also a great burden of treating weight related chronic diseases such as diabetes and cardiovascular diseases [6].



Changes due to urbanization

The international obesity task force estimates that upto 1.7 billion people may be exposed to weight related health risks which includes Asian population with a BMI of 23 or more[7]. Recently, obese populations have also been shown to be vulnerable to oxidative stress. Obesity is an independent risk factor for a reduction in erythrocyte antioxidant enzyme activities and is associated with lower levels of serum antioxidants such as vit. E and B Carotene. It has also been put forward, that production of reactive oxygen species (ROS) is increased significantly in adipose tissue of non diabetic obese and accompanied by decreased antioxidative enzymes only in fat tissues. Inhibition of ROS production attenuated the dysregulation of adipocytokines and improved insulin resistance, diabetes and hyperlipidemia[8].

Obesity is the most powerful environmental risk factor for type 2 diabetes mellitus also and BMI is a standard predictor of diabetic status. The prevalence of diabetes is 2.9 times higher in overweight (BMI $\geq$ 27.8 in men and $\geq$ 27.3 in women) than in normal weight subjects[9, 10]. The conversion to diabetes is enhanced by the low thresholds for the risk factors such as age, BMI and upper body adiposity. With a high genetic predisposition and the high susceptibility to the environmental insults, the Indian population faces a high risk for diabetes and its associated complications. Diabetologists are now observing a sharp increase in type 2 DM primarily because of increases in sedentary life style and obesity[11, 12].

Also, Obesity and type 2 diabetes both are independent risk factors for hypertension and dyslipidemia. Multiple modifications of serum lipids and lipoproteins as evidenced in this study are frequently noted in overweight/obese individuals. The most common modifications are hypertriglyceridemia and decreased HDL-C levels. There is a strong negative correlation between obesity and HDL-C levels. It has been postulated that there is a decrease of approximately 0.4 mg/dl of HDL-C with each Kg/m^2 increment of BMI[13, 14].

Aims and objectives

The present study was planned to assess:

- Obesity as an independent risk factor for decreased activity of antioxidant enzymes in humans,
- Its role in complicating glucose and lipid metabolism in type 2 diabetic subjects
- To evaluate the effect of obesity on glucose and lipid levels in type 2 diabetics.

Material and methods

The study was conducted on obese and non-obese type 2 diabetic subjects as well as obese non diabetic subjects of either sex, middle aged admitted in wards and attending OPD of J.L.N. Medical College and Associated Group of Hospitals. The results were compared with 25 age matched healthy controls.

The subjects were grouped as follows –

Group I (n = 50):

Subgroups: (a) 25 obese type 2 diabetic.

(b) 25 obese with different grades of obesity (30-50 kg/m^2) with no history of type 2 diabetes, hypertension and hyperlipidemia.

Group II (n = 25): Non obese type 2 diabetic subjects.

Group III (n = 25): Healthy controls

Fasting blood samples were collected by venipuncture in vacutainers. Plain vacutainers were employed for assay of serum lipid profile, EDTA vacutainers for assay of plasma glucose and antioxidant enzymes.

Following parameters were assessed –

1. BMI (Body mass index): A ratio of weight and square of height (expressed as kg/m^2).
2. Plasma Glucose (fasting and post prandial):
   Method: Caraway W.T., Bergmayer H.V.[15]
3. Lipid Profile :
   - Serum cholesterol (CHO)
     Method – Meiattini F et al.[16]
   - Serum triglycerides (TG)

Method – Buccolo G et al. [17]

- Serum High density lipoprotein cholesterol (HDL-C)
  Method – Allain CC et al.[18]
- Serum Very low density lipoprotein = VLDL and
- Low density lipoprotein – cholesterol = LDL-C calculated according to Friedwald's equation.[19]
  VLDL = TG/5
  LDL – C = CHO – (HDL-C + TG/5)

4. Super Oxide Dismutase (SOD) :
   Method – McCord and Fridovich.[20]
5. Glutathione Peroxidase (GPx)
   Method ─ Paglia and Valentine.[21]

Statistical analysis

Results were shown as mean ± standard deviation (SD). Changes in values of controls and SCH patients were analysed by student's t test. Values $p<0.05$ were accepted as statistically significant.

Observations

Table 1

Activities of Erythrocyte SOD and GPx in Normal and Obese Non Diabetic Subjects

BMI (Kg/m^2)	**SOD (Units/gHb) Mean ± SD**	**GPx (Units/gHb) Mean ± SD**
19-22 (n=25) (Healthy Controls)	1443.45 ± 176.84[a]	95.1 ± 3.6[a*]
30-39 (n=15) (Obese non diabetics)	1218.0 ± 31.0[b]	92.3 ± 3.2[b*]

40-49 (n=10) (Obese non diabetics)	986.0 ± 25.0[c]	80.8 ± 7.2[c*]

a and b, a* and b* show $P < 0.001$, a and c, a* and c* show $P < 0.0001$

Figure 1

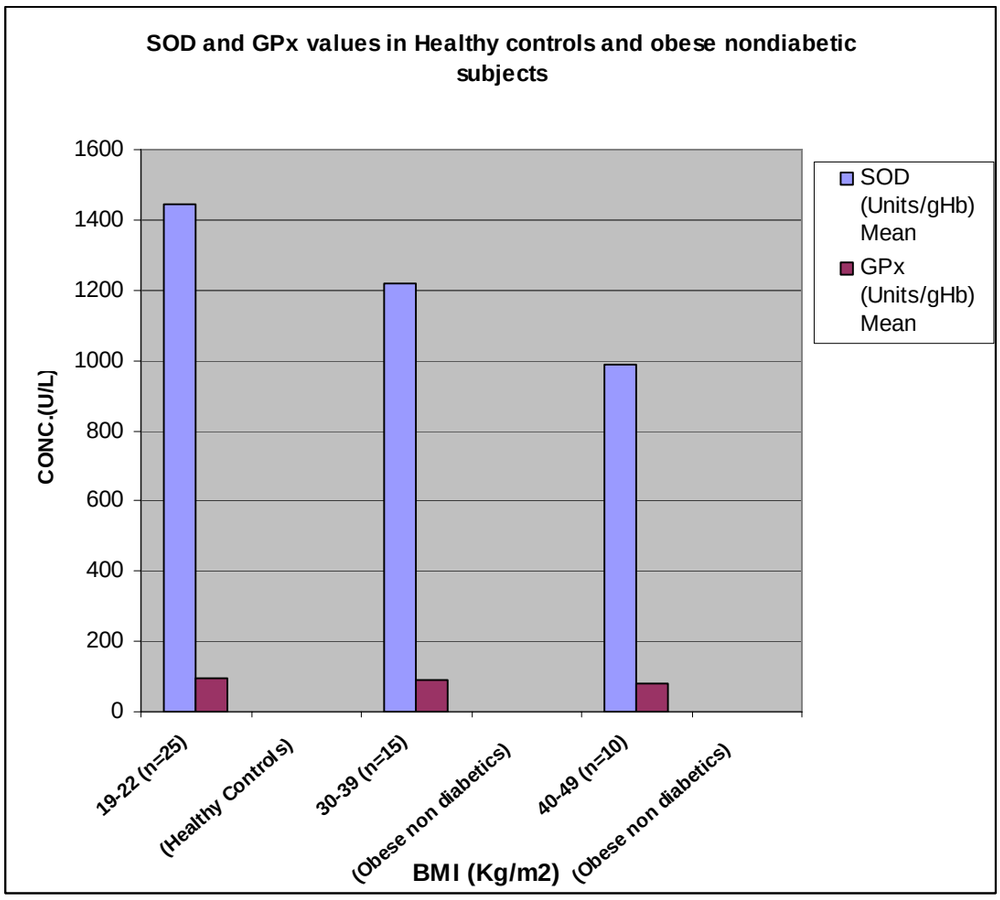


Table 2

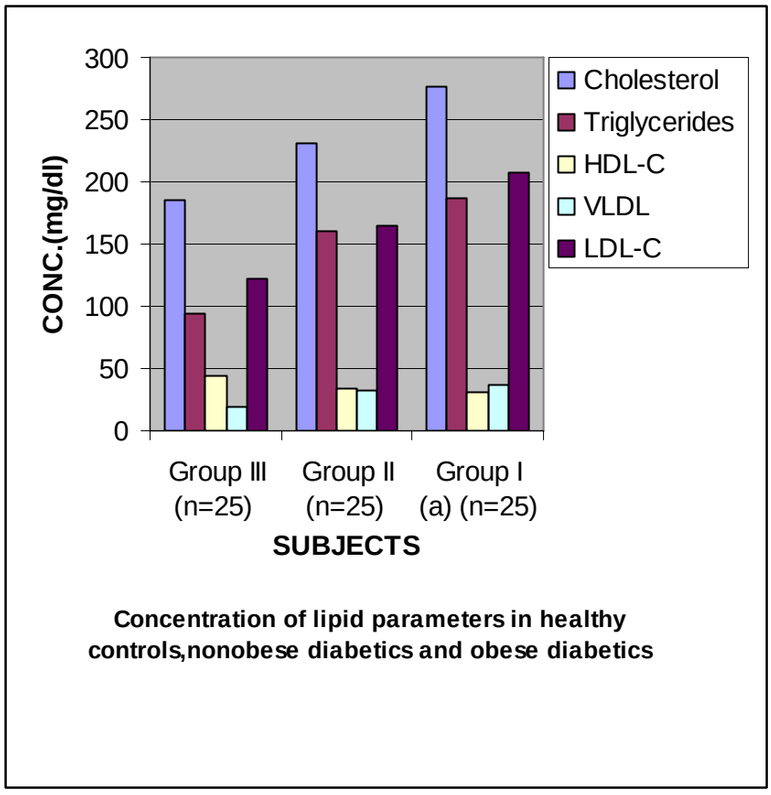
Levels of various Biochemical Parameters assessed in Lipid Profile in Various Groups of Subjects (Healthy Controls, Non Obese type 2 Diabetics and Obese type 2 Diabetics)

Parameters (mg/dl)	**Group III (n=25) Mean ± SD**	**Group II (n=25) Mean ± SD**	**Group I (a) (n=25) Mean ± SD**
Cholesterol	184.68 ± 4.52º	231.0 ± 8.43*	276.03 ± 4.62#
Triglycerides	94.10 ± 5.65º	160.0 ± 5.53*	186.6 ± 4.02#
HDL-C	44.28 ± 2.36º	33.94 ± 1.37*	30.98 ± 0.92#
VLDL	18.82 ± 1.13º	31.69 ± 1.09*	37.3 ± 0.76#
LDL-C	121.58 ± 10.12	165.29 ± 6.69*	207.75 ± 9.23#

º vs* $P < 0.001$(Very significant)

* vs #, º vs # $P < 0.0001$(Highly significant)

Figure 2



Concentration of lipid parameters in healthy controls,nonobese diabetics and obese diabetics

Table 3

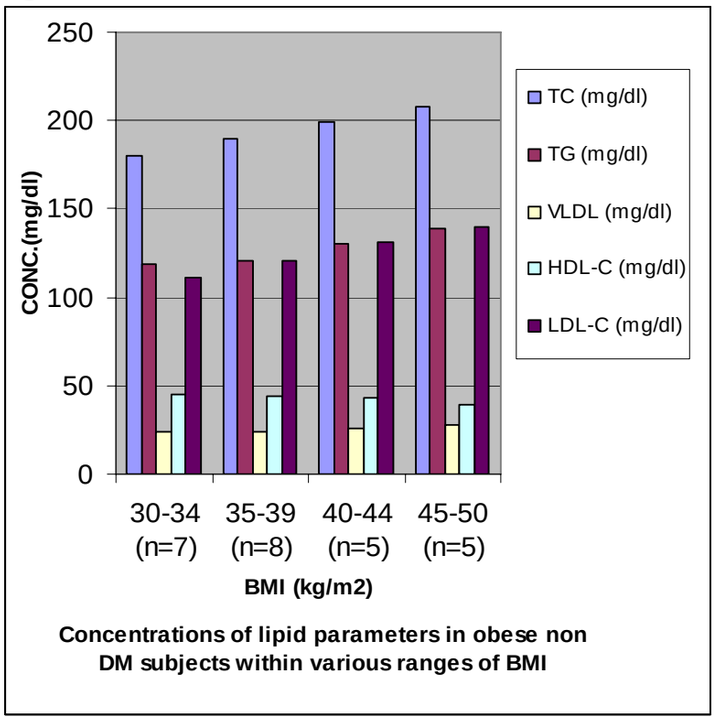
Concentrations (expressed as mean ± SD) of lipid profile parameters in obese non diabetic subjects (group IIb) in various ranges of BMI

BMI (kg/m^2)	TC (mg/dl)	TG (mg/dl)	VLDL (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
30-34[a] (n=7)	180.0±10.3	119.0±10.3	23.7±2.06	45.2±1.56	111.0±11.0
35-39[b] (n=8)	190.0±7.13	121.0±7.13	24.2±1.42	44.4±1.41	121.0±7.56
40-44[c] (n=5)	199.0±6.15	130.0±5.36	25.9±1.05	42.7±1.08	131.0±6.92
45-50[d] (n=5)	208.0±4.04	139.0±5.56	27.7±	39.5±1.60	140.0±4.89

P values a Vs b TC, TG, VLDL, HDL-C, LDL-C are 0.04 (S), 0.55 (NS), 0.54 (NS), 0.30 (NS), 0.05(S)
P values a Vs c TC, TG, VLDL, HDL-C, LDL-C are 0.004 (VS), 0.05 (S), 0.05 (S), 0.01 (S), 0.005 (S)
P values a Vs d TC, TG, VLDL HDL-C, LDL-C are 0.0002 (HS), 0.002(VS), 0.002 (VS), < 0.0001 (HS), 0.0002 (HS).
P values b Vs c TC, TG, VLDL, HDL –C, LDL-C are 0.04 (S), 0.05 (S), 0.05 (S), 0.03 (S), 0.05 (S).
P values b Vs d TC, TG, VLDL, HDL-C, LDL-C are 0.0004 (HS), 0.0008 (HS), 0.0008 (HS), 0.0001 (HS), 0.0004 (HS).
P values c Vs d TC, TG, VLDL, HDL-C, LDL-C are 0.03 (S), 0.03 (S), 0.03 (S), 0.006 (VS), 0.03 (S).

S = Significant
NS = Non significant
VS = Very significant
HS = Highly significant

Figure 3



Concentrations of lipid parameters in obese non DM subjects within various ranges of BMI

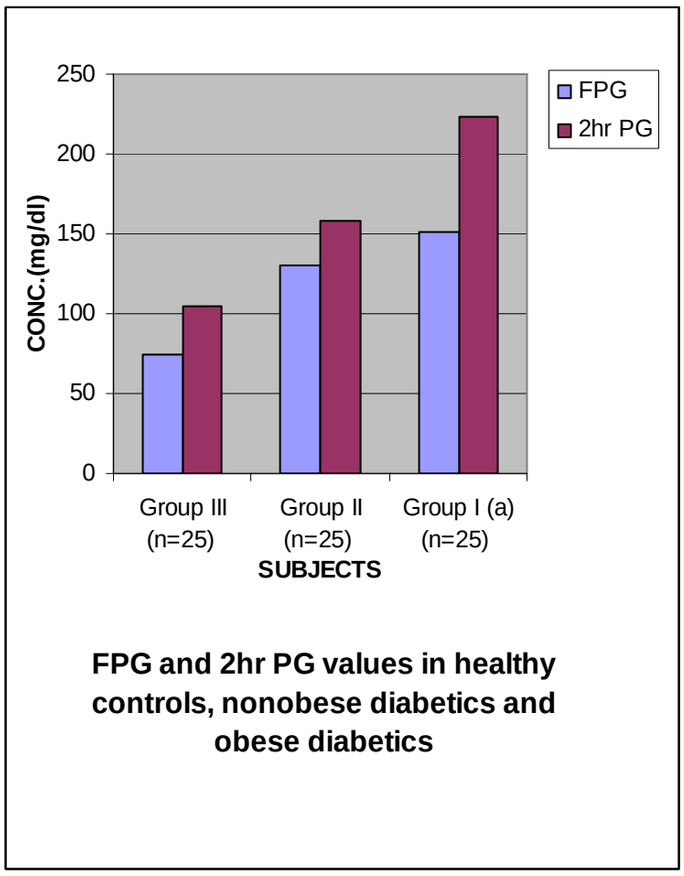
Table 4

Values of Fasting and Post Prandial Plasma Glucose (FPG, 2hr PG) in Healthy Controls, Non-Obese type 2 Diabetics and Obese type 2 Diabetics

Parameters (mg/dl)	**Group III (n=25) Mean ± SD**	**Group II (n=25) Mean ± SD**	**Group I (a) (n=25) Mean ± SD**
FPG	74.7 ± 6.5	130.34 ± 3.59*	151.7 ± 21.8#
2hr PG	104.3 ± 5.2	158.2 ± 8.9*	223.03 ± 5.09#

* and # $P < 0.0001$ (Highly significant)

Figure 4



FPG and 2hr PG values in healthy controls, nonobese diabetics and obese diabetics

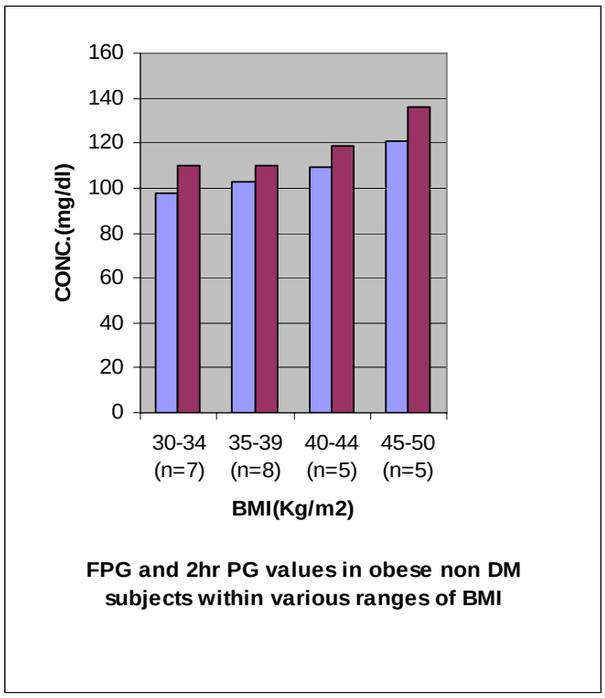
Table 5

Concentrations (expressed as mean ± SD) of FPG and 2hr PG in obese non diabetic subjects (group IIb) in various ranges of BMI

BMI (kg/m^2)	**FPG (mg/dl)**	**P value**	**2 hr PG (mg/dl)**	**P value**
30-34[a] (n=7)	97.5±6.80	a vs b 0.08 (NS)	110.0±6.62	a vs b 0.84 (NS)
35-39[b] (n=8)	103.0±4.53	a vs c 0.03 (S)	110.0±5.36	a vs c 0.08 (NS)
		a vs d 0.001 (VS)		a vs d 0.0005 (HS)
40-44[c] (n=5)	109.0±8.38	b vs c 0.13 (NS)	119.0±9.64	b vs c 0.05 (S)
		b vs d 0.002 (VS)		b vs d 0.0002 (HS)
45-50[d] (n=5)	121.0±11.8	c vs d 0.09 (NS)	136.0±11.0	c vs d 0.03 (S)

S = Significant
NS = Non significant
VS = Very significant
HS = Highly significant

Figure 5



FPG and 2hr PG values in obese non DM subjects within various ranges of BMI

Results

The results of the study that is values of antioxidant enzymes SOD and GPx, Lipid profile and Glucose in the subjects are given in tables 1-5 respectively and in figures1-5.

Table 1 (Figure1) shows an inverse relationship between BMI and erythrocyte SOD activity. The mean erythrocyte SOD activity of subjects with healthy body weight (1443.45 ± 176.84 units/g Hb) was significantly higher (P<0.001) than in subjects with BMI greater than 30 kg/m^2 (1218.0 ± 31.0 units/g Hb). The table also shows that subjects with BMI above 40 kg/m^2 have the lowest activity of erythrocyte SOD (986.0 ± 25.0 units/g Hb). Table 1 also shows an inverse relationship between the erythrocyte cytoprotective enzyme GPX and BMI. The activity of this enzyme in individuals with healthy BMI (95.1±3.6 units/g Hb) was significantly higher (P<0.001) than the value in those with BMI greater than 30 kg/m^2 (92.3±3.2 units/g Hb). Subjects with BMI greater than 40 kg/m^2 had the least activity of this enzyme (80.8 ± 7.2units/g Hb). Thus the results

support the role of obesity in decreasing the activities of antioxidant enzymes or in other terms enhancing oxidative stress.

In Table 2 (Figure 2) the values of various biochemical parameters measured in lipid profile showed a highly significant pattern in group II ($p< 0.001$) and Group I(a) ($p<0.0001$) subjects compared to healthy controls. Also, the values were significantly higher ($P < 0.0001$) in group I (a) compared to group II supporting the effect of obesity in further impairing the lipid levels in type 2 diabetics.

In Table 3 (Figure 3) the values of TC, TG, VLDL, HDL-C and LDL-C showed significantly increasing patterns with increase in BMI. Significantly high values for TC and LDL-C were obtained in group IIb subjects with BMI 35-39 Kg/ m^2 compared to those with BMI 30-34Kg/ m^2 (0.04, 0.05).Further, subjects with BMI 40-44 Kg/ m^2 showed significantly high values for all lipid parameters (0.004, 0.05, 0.05, 0.01, 0.005) compared to those with BMI 30-34Kg/ m^2.Significant differences in values were obtained in subjects with BMI 45-50 Kg/ m^2 (0.0002, 0.002, 0.002, < 0.0001, 0.0002) compared to those with BMI 30-34Kg/ m^2.

Even when subjects with BMI 35-39Kg/ m^2 were compared to those with BMI 40 - 44 Kg/ m^2 significant differences in values were obtained (0.04, 0.05, 0.05, 0.03, 0.05). Further, on comparing subjects with BMI 35-39Kg/ m^2 with BMI 45 - 50 Kg/ m^2 significant differences in values were obtained (0.0004, 0.0008, 0.0008, 0.0001, 0.0004).Values for subjects with BMI 45 - 50 Kg/ m^2 were significantly higher when compared to subjects with BMI 40-44 Kg/ m^2 (0.03, 0.03, 0.03, 0.006,0.03).

In table 4 (figure 4) the plasma glucose values (FPG and 2hr PG) were significantly higher ($P < 0.0001$) in group I (a) compared to group II reflecting the effect of obesity in impairing the glucose levels further, in subjects with type 2 diabetes.

In table 5 (figure 5) the FPG and 2hr PG values in obese non diabetic subjects with BMI 40-44 Kg/ m^2,45-50 Kg/m^2 showed significantly higher values compared to subjects with BMI

30-34 Kg/ m^2 [FPG:0.03, 0.001 ;2hrPG: 0.08(not quite significant),0.0005]. Further, 2hr PG values showed a significant pattern in subjects with BMI 40-44 Kg/ m^2 compared to those with BMI 35-39 Kg/ m^2(0.05) and 45-50 Kg/ m^2(0.03).FPG and 2hr PG values were higher in subjects with BMI 45-50 Kg/ m^2 compared to subjects with BMI 35-39 Kg/ m^2 (0.002, 0.0002).

Discussion

The obesity epidemic is of considerable importance since it runs parallel to the type 2 DM and metabolic syndrome epidemic, we are currently experiencing. It is important to single out obesity as it plays an important role in the development of abnormalities related to glucose and lipid metabolism[22].

In our study we noted a decrease in levels of antioxidant enzymes viz. SOD and Gpx with increase in BMI. The decrease was significant in subjects with BMI 40-49 Kg/m^2 ($P < 0.0001$) compared to subjects with BMI 19-22 Kg/m^2. The decrease in SOD and Gpx activities in obese could be due to increased H_2O_2 production in adipose tissue of obese.

SOD is believed to play a major role in the metabolism of reactive oxygen species (ROS). It is the first enzyme involved in the destruction of superoxide (O_2^-) anion radicals. It converts O_2^- into hydrogen peroxide (H_2O_2). Animal cells contain two intracellular forms of SOD, the cytoplasmic or copper zinc form (Cu – Zn SOD) and mitochondrial or manganese form (Mn-SOD). This enzyme is the first line of defense against O_2^- anion radicals and can be induced rapidly in some conditions such as exposure to oxidative stress (OS) of cells or organs[23, 24].

H_2O_2 is metabolized by Gpx in synergy with glutathione reductase (GSH). Gpx has a much higher affinity for H_2O_2 than catalase suggesting that H_2O_2 is mainly degraded by Gpx under normal condition[23,24].Furukawa et al., (2004) suggested that adipose tissue is the major source of elevated plasma ROS. In normal conditions a state of redox homeostasis

is present which is the normal physiologic process of reduction and oxidation in order to repair unstable, damaging ROS which include toxic oxygen free radicals [O_2^- and OH^- (hydroxyl radical)], the highly unstable pro-oxidant oxygen non radicals (H_2O_2, singlet oxygen and organic analogues). OS implies a loss of redox homeostasis with an excess of ROS. OS is associated with an overproduction of ROS as well as an impairment of antioxidant defensive capacity as found in type 2 DM, metabolic syndrome and obesity alone.[25]

Obesity increases the OS by three possible mechanisms. Firstly, it increases the mechanical and metabolic load on the myocardium, thus increasing myocardial oxygen consumption. A negative consequence of the elevated myocardial oxygen consumption is the production of ROS such as O_2^-, hydroxyl radical and hydrogen peroxides from the increased mitochondrial respiration. Leakage of electrons out of the mitochondrial election transport chain promotes a one electron reduction of molecular oxygen resulting in the formation of O_2^- radicals.[26]

The second mechanism by which obesity can independently cause OS is by progressive and cumulative cell injury resulting from pressure from the large body mass. Cell injury causes the release of cytokines especially tumour necrosis factor alpha (TNF- α) which generates ROS from the tissues [27].

A third possible mechanism is through diet which is probably a predominant cause in India. Nutritional obesity implies the consumption of hyperlipidemic diets which may be involved in oxygen metabolism. Double bonds in the fatty acid molecules are vulnerable to oxidation reactions and may consequently cause lipid peroxidation.[28]

Thus, the decreased values of SOD and GPx observed in our study could be due to increased OS caused by obesity which causes stimulation of antioxidant enzymes. But over a period of time the stores of antioxidant enzymes are depleted and cannot keep pace with increasing OS.

In our study we also observed a significant increase in TC, TG, VLDL-C, LDL-C values (P = 0.0002, P = 0.002, P = 0.002, P = 0.0002) in obese non diabetics with BMI 45-49 kg/m^2 compared to those with BMI 30-34 kg/m^2.

Further, comparison of obese diabetic subjects (Group IIa) with obese non diabetics (Group IIb) yielded significant results suggesting that with obesity insulin resistance worsen and dyslipidemia in type 2 diabetics impairs further[29, 30]. This causes raised TC, TG, VLDL-C, LDL-C and lower levels of HDL-C in obese diabetics compared to obese non diabetes. According to Grundy (2005) dyslipidemia associated with obesity is multi-factorial, and is frequently associated with a cluster of interrelated cardiovascular disease risk factors. Obesity is a critical determinant of dyslipidemia and operates through a number of metabolic influences that include reduced insulin sensitivity and changes in fatty acid metabolism. Variations in the nature and magnitude of the dyslipidemia are due to the interaction of genetic factors with environmental influences most notably diet and physical activity, and possibly stress[31].

Among the major effects of excess adiposity on plasma lipoproteins are increases in levels of TG rich VLDL particles. Both adipocyte derived fatty acids and cytokines, or adipokines, can promote increased TG synthesis, leading to increased hepatic secretion of TG enriched VLDL. Plasma VLDL levels can increase further as a result of reduced lipolysis and clearance due to the lower peripheral activity of lipoprotein lipase (LPL) associated with adiposity. Partially lipolysed VLDL remnants can then return to the liver, adding to the TG pool available for VLDL secretion[32].

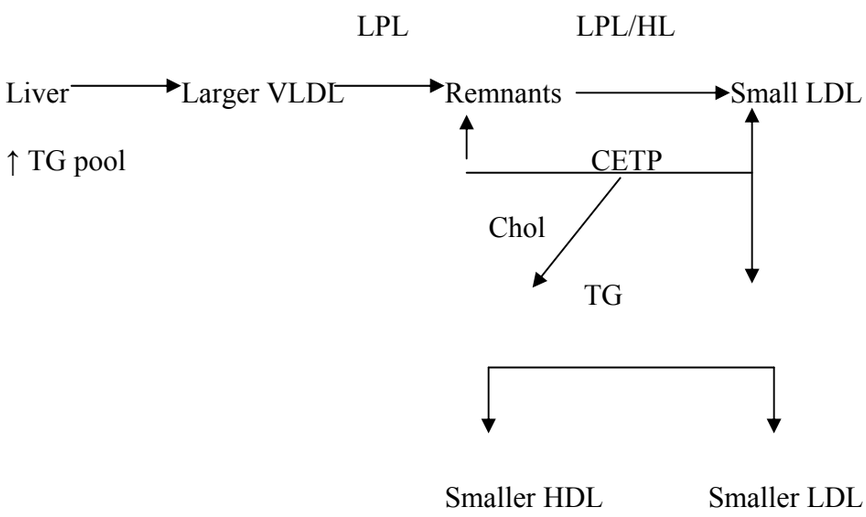
As TG level increases in obese individuals the diameter of major LDL species decline. The mechanism for increased LDL according to Berneis (2002) is that a higher level of plasma TG is associated with larger VLDL particles are lipolysed less efficiently by LPL. This gives rise to remnant particles. These remnants have increased content of the apoprotein C III. Their slow lipolysis lead to reduced receptor mediated plasma clearance[33].

The remnants are further lipolysed by the combined action of LPL and hepatic lipase (HL) a process mediated by cholesterol ester transfer protein (CETP). The resulting TG is, in addition delipidated and remodeled to form smaller, lipid depleted LDL. These particles have lower affinity for LDL receptor. Moreover, higher levels of remnant particles lead to increased exchange of TG for cholesterol in both LDL and HDL, a process mediated by CETP. TG rich LDLS and HDLS are degraded further by HL, leading to yet smaller LDLs and to smaller and less stable HDLs that are more rapidly catabolised, resulting in reduced HDL cholesterol (Fig. 6). There is a strong negative correlation between obesity and HDL-C levels with a decrease of approximately 0.4 mg/dl of HDL-C with each kg/m^2 increment of BMI[33, 34].

Factors causing dyslipidemia:

- High carbohydrate diet
- Adiposity
- Insulin resistance
- Genetic predisposition

Fig 6: DYSLIPIDEMIA OF OBESITY



CETP = Cholesteryl ester transfer protein HDL = High density lipoprotein

LDL = Low density lipoprotein HL = Hepatic lipase

Chol = Cholesterol

TG = Triglycerides

LPL = Lipoprotein lipase

According to Williams (1997) increased BMI is associated with shift from larger to smaller LDL particles. They suggested an association of body fat with atherogenic dyslipidemia[35]. This is consistent with the findings of our study. We also observed an abnormal lipid profile with increasing BMI values in obese non diabetics.

In a recent study by Redinger (2007) excessive storage of fatty acid as TG within adipocytes creates obesity. This eventually leads to the release of excessive fatty acids from enhanced lipolysis, which is stimulated by the enhanced sympathetic state existing in obesity[36]. The release of these excessive free fatty acids (FFAs) then incites

lipotoxicity, as lipids and their metabolites create oxidant stress to the endoplasmic reticulum and mitochondria. This affects adipose as well as non adipose tissue, accounting for its pathophysiology in many organs such as the liver and pancreas, and in metabolic syndrome[37, 38]. The FFAs released from excessively stored TG deposits also inhibit lipogenesis, preventing adequate clearance of serum TG levels that contribute to hypertriglyceridemia[39].

The above mechanism probably causes insulin receptor dysfunction. This results in an insulin resistant state that creates hyperglycemia with compensated gluconeogenesis[39, 40]. The above explanation supports the results of our study as elevated FPG and 2 hr PG levels were observed in obese non diabetics.

The obesity induced hyperglycemic state also increases hepatic glucose production. This accentuates the insulin resistance in obese as BMI increases. It is also decreases utilization of insulin stimulated muscle glucose contributing further to hyperglycemia[39, 40].

A significant pattern of increase in levels of FPG and 2 hr PG was observed in obese non diabetic subjects with increase in BMI from 30 to 50 kg/m^2. This can be substantiated by the significant results obtained an comparing obese subjects with BMI 30-34 kg/m^2 with subjects in BMI ranges 35-39 kg/m^2, 40-44 kg/m^2 and 45-50 kg/m^2 respectively ($P = 0.08$, $P = 0.03$, $P = 0.001$ for FPG values) ($P = 0.84$, $P = 0.08$, $P = 0.0005$ for 2 hr PG)(Table5).

The above results are in agreement with the following concept that resistance to insulin action augments with increasing severity of obesity. With passage of time the functional capacity of the insulin secreting cells of islets of langerhans first increases, as a result of hypertrophy and perhaps limited hyperplasia. When the total functional capacity of the system is reached the decompensation and perhaps true exhaustion of the

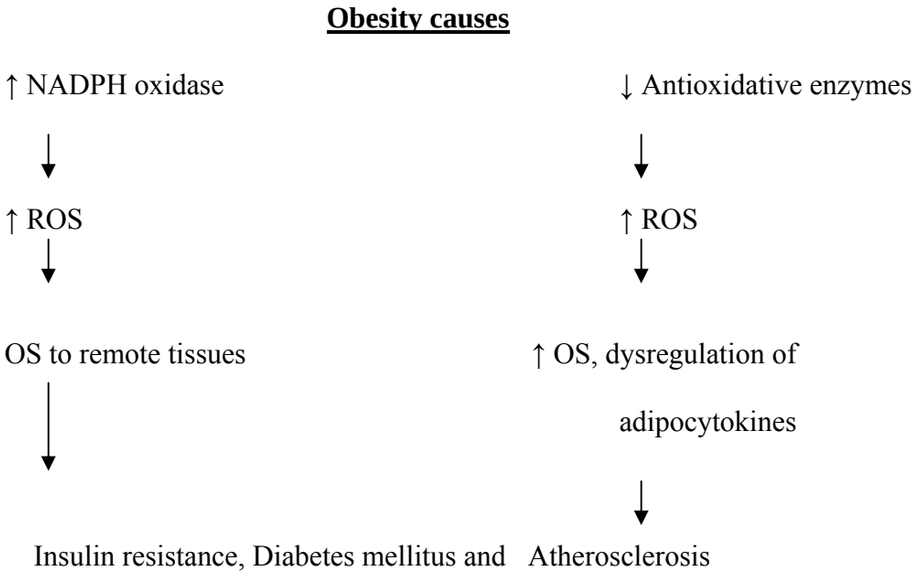
insulin producing ability occurs. This results in a gradual yet continuous deterioration of glucose intolerance in the obese subjects who are likely to end up with type 2 DM[41].

The above mechanism illustrates the role of obesity in causing DM. However, also in our study the obese diabetic subjects (group IIa) showed a more atherogenic lipid profile and also significantly higher FPG and 2 hr PG values compared to obese non diabetic subjects. This suggests that the above discussed effects of obesity on lipids and glucose are amplified in diabetics with obesity.

The decreased levels of antioxidant enzymes observed in obese non diabetics may also play a role in impairing glucose tolerance in these subjects. We have discussed previously that obesity causes increases in OS. It is known that OS impairs both insulin secretion by pancreatic β cells, glucose transport in muscle and adipose tissue [23].

The possible mechanism could be that increased production of ROS is accompanied by augmented expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and decreased expression of antioxidative enzymes and OS. This causes dysregulated production of adipocytokines (fat derived hormones). Excessive and long term exposure to ROS reduces insulin sensitivity and impairs glucose as well as lipid metabolism[23] (Fig. 7).

Fig.7. ROS production in accumulated fat contributes to insulin resistance, DM and atherosclerosis



Conclusion

From the study it is indicated that obesity is an independent risk factor to cause decreased activity of antioxidant enzymes. Obesity is an exaggeration of normal adiposity and is a central player in the pathophysiology of DM, insulin resistance, dyslipidemia, hypertension and atherosclerosis. Obesity is a major contributor to the metabolic dysfunction involving lipid and glucose as well as in complicating the clinical symptoms in subjects already suffering from type 2 diabetes. Thus, it may be suggested that weight control is a prerequisite for an obese so as to avoid the associated metabolic complications. It is also of considerable concern in India as urbanisation has resulted in several changes in life style which is causing a clustering of cardiovascular risk factors namely central adiposity, obesity, hyperinsulinemia, dyslipidemia, hypertension and glucose intolerance.

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