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Study of Thyroid Dysfunction in Patients with Metabolic Syndrome

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Abstract
Introduction : *Metabolic syndrome predisposes men and women to premature coronary artery disease. Thyroid functions affect metabolic syndrome parameters including high density lipoprotein (HDL) cholesterol, triglycerides, blood pressure & plasma glucose. There is a need for study to explore the association between thyroid dysfunction & components of metabolic syndrome. This study was conducted to study the pattern of thyroid dysfunction among metabolic syndrome patients.*
Aims & Objectives :
1) To study thyroid dysfunction in patients with metabolic syndrome.
2) To analyse the association of thyroid dysfunction and metabolic syndrome.
Methods : *Study was done in M S Ramaiah Hospital during October 2012 to August 2014. 108 subjects were chosen comprising 54 cases of metabolic syndrome and 54 controls. Patients were recruited into the study group after satisfying the IDF criteria of metabolic syndrome, considering the inclusion and exclusion criteria.*
Results :*Among controls, 92.6 % were Euthyroid, 5.6% were Hypothyroid, 1.9% were Sub clinical hypothyroid. Among cases 64.8% were Euthyroid. Thyroid dysfunction was prevalent among 35.2% metabolic syndrome patients. Sub clinical hypothyroidism was seen in 24.1% patients & overt hypothyroidism in 11.1% patients.*
Interpretation and Conclusion :*This study clearly shows that, the prevalence of thyroid dysfunction in metabolic syndrome patients is higher than normal subjects. As metabolic syndrome & hypothyroidism are independent risk factors for the same disease process namely cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk. Hence there is a need for screening for thyroid dysfunction in metabolic syndrome patients.*
Key Words: *Metabolic syndrome, Thyroid dysfunction, Subclinical Hypothyroidism.*

I. Introduction

The metabolic syndrome consists of a central distribution of adiposity, insulin resistance, elevations in plasma free fatty acid levels, impaired glucose tolerance, hypertension, dyslipidemia and an abnormal procoagulant state. Many features of this syndrome are known to predispose men and women to premature coronary artery disease[1].Epidemiology shows increased prevalence of metabolic syndrome. Subclinical hypothyroidism is an asymptomatic condition with high serum thyroid stimulating hormone (TSH) and normal free thyroid hormone levels. It is a prevalent condition among adult population which is frequently overlooked[1].Subclinical hypothyroidism has also been suggested as a risk factor for atherosclerosis, hyperlipidemia, hypertension, low grade inflammation & hypercoagulability. Thyroid functions affect metabolic syndrome parameters including high density lipoprotein (HDL) cholesterol, triglycerides, blood pressure & plasma glucose[1].As metabolic syndrome & hypothyroidism are independent risk factors for the same disease process namely cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk.Hence this study was conducted to explore the association between thyroid dysfunction & components of metabolic syndrome

II. Aims & objectives

1) To study thyroid dysfunction in patients with metabolic syndrome.
2) To find out the association of thyroid dysfunction and metabolic syndrome.

III. Materials And Methods

Source of data:The study was conducted in MS Ramaiah Hospital between October 2012 and August 2014. Population satisfying inclusion criteria were enrolled in this study after obtaining written informed consent.
Method of collection of data: Method of collection of data was done by taking detailed history, clinical examination and laboratory investigations through proforma specially designed for this study, after taking the informed consent. All cases were subjected to following investigations

FBS, PPBS, HbA1C, Fasting Lipid profile, TSH, FT4 if abnormal TSH
Waist circumference- measured in a horizontal plane midway between the inferior margin of the ribs and superior border of the iliac crest
BMI calculated as: - wt in kg/ht in m^2
Blood pressures will be recorded after at least 5 minutes of rest in both arms sitting/supine position
Based on the literature reference[2] Sample size is 108, calculated using n-master software with 54 cases and 54 controls.

Inclusion Criteria
Patients satisfying the IDF consensus worldwide definition of the metabolic syndrome (2006)
1.Central obesity - defined as waist circumference with ethnicity specific values for south Asians: ≥90 cm for Men and ≥80cm for women.and any two of the following:
2.Raised triglycerides: > 150 mg/dL, or specific treatment for this lipid abnormality.
3.Reduced HDL cholesterol: < 40 mg/dL in males,< 50 mg/dL in females, or specific treatment for this lipid abnormality
4.Raised blood pressure: systolic BP >130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension.
5.Raised fasting plasma glucose :(FPG) ≥100 mg /dL, or previously diagnosed type 2 diabetes[1].

Exclusion criteria
1. Known hypothyroid or sub-clinical hypothyroid or hyperthyroid patients or on treatment.
2. Individual less than 18 years age.
3. Patients with liver disorders, renal disorders, congestive cardiac failure, pregnant women.

Statistical analysis
- Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made.

1) Dependent variables should be normally distributed
2) Samples drawn from the population should be random & samples of the cases should be independent
Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.
Descriptive statistics of subclinical hypothyroidism & hypothyroidism among metabolic syndrome patients was analyzed & expressed in terms of proportions (%) & its 95% confidence interval was analyzed.

We classified patients as SCH, overt hypothyroidism, hyperthyroidism, subclinical hyperthyroid based on the definitions as per ATA guidelines Subclinical Hypothyroidism was defined as TSH-4.5 to 10 with normal FT4 Overt Hypothyroidism-TSH>10 with low FT4 Hyperthyroidism-<0.45 TSH with raised FT4 Subclinical Hyperthyroidism<0.45 TSH with normal FT4

INVESTIGATION	NORMAL VALUE
PPBS	< 140 mg/dl
Serum FT4	0.93 – 1.7 ng/dl
Serum TSH	0.45 – 4.5 μIU/ml
Serum TG	< 150 mg/dl
Serum HDL	> 40 mg/dl

C) Results

In our study, 108 subjects were recruited comprising 54 cases of metabolic syndrome and 54 controls. There were 38.8% males and 61.2% females in the study group whereas 27.7% males and 72.3% females in the control group (Table 1). The mean age was 54.87±12.68 yrs in cases and 54.13±6.16 yrs in the control group (Table 2). Most of cases and controls were distributed among 41- 60 years.

The mean waist circumference in the cases was 89.07±5.31 cm and 69.07±4.73 cm in the control group. The mean BMI was 29.77±3.17 kg/m^2 in the study group and 23.12±1.21 kg/m^2 in the control group

(Table 3). Most of cases had a BMI between 25-29.9 kg/m^2 (55.6%), controls had between 18.5-24.9 kg/m^2 (96.3%).The mean duration of diabetes was 6.22±6.56 yrs. A total 51 out of 54 cases (94.4%) satisfied the IDF criteria of FPG>100 mg/dl inferring impaired fasting glucose or type 2 diabetes. The mean FBS in the cases was 187.02±59.86 mg/dl & in the controls was 80.76±9.55 mg/dl. 88.9% of the cases had FBS >126 (Fig 1).The mean PPBS in the cases was 301.63±101.91 mg/dl & 87.0 % had PPBS >200 (Fig 2). The mean HbA1C in cases was : 8.70±2.07 %. These observations suggest a high prevalence of type 2 diabetes in patients with metabolic syndrome.The mean duration of hypertension was 4.15±5.21 years in the cases. The mean systolic blood pressure (SBP) in cases was 148.26±16.83 mmHg and 112.96±5.64 mmHg in controls (Table 4). The mean diastolic blood pressure was 88.81±7.35 mmHg and 74.22±5.08 mmHg in cases and controls respectively (Table 5). A total of 46 out of 54 cases satisfied the IDF criteria of SBP>130 mmHg.

The mean duration of dyslipidemia in cases was 2.93±2.41 years. The mean triglyceride was 240.35±122.01mg/dl, HDL was 33.87±11.74mg/dl in cases. A total of 49 out of 54 cases had TG>150. Total of 48 out of 54 cases had HDL <40mg/dl for males and <50mg/dl for females. The mean triglyceride and HDL was 133.35±9.93mg/dl & 55.01±6.04mg/dl respectively in the control group (Fig 3). The mean TSH in the control group was 2.81±2.95 mIU/ml. The mean TSH in the cases was 5.75±9.84 mIU/ml (Table 6).

Among controls, 92.6 % were Euthyroid, 5.6% were Hypothyroid, 1.9% were Sub clinical hypothyroid.In this study, 64.8% were Euthyroid. Thyroid dysfunction was prevalent among 35.2% metabolic syndrome patients. Sub clinical hypothyroidism was seen in 24.1%, overt hypothyroidism in 11.1% cases (Table 7).

	CASES	CONTROLS
MALES	21(38.8%)	15(27.7%)
FEMALES	33(61.2%)	39(72.3%)
TOTAL	54	54

Table No 1 :Sex Distribution Of Cases & Controls

Age in years	**Cases**		**Controls**	
	No	**%**	**No**	**%**
21-30	1	1.9	4	7.4
31-40	6	11.1	8	14.8
41-50	15	27.8	7	13.0
51-60	14	25.9	20	37.0
61-70	12	22.2	6	11.1
71-80	5	9.3	5	9.3
>80	1	1.9	4	7.4
Total	54	100.0	54	100.0
Mean ± SD	54.87±12.68		54.13±6.16	

Table No 2 : Age Distribution Of Patients Studied

BMI (kg/m^2)	**Cases**		**Controls**	
	No	**%**	**No**	**%**
<18.5	0	0.0	0	0.0
18.5-24.9	1	1.9	52	96.3
25-29.9	30	55.6	2	3.7
30-34.9	19	35.2	0	0.0
35-39.9	4	7.4	0	0.0
>40	0	0.0	0	0.0
Total	54	100.0	54	100.0

Table No 3 : BMI Distribution Of Cases & Controls

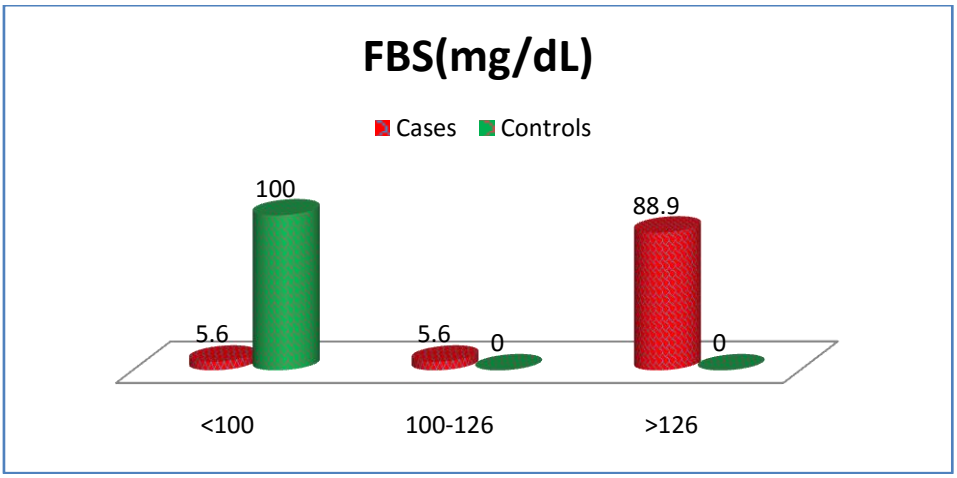

Fig No 1 : FBS among controls & cases

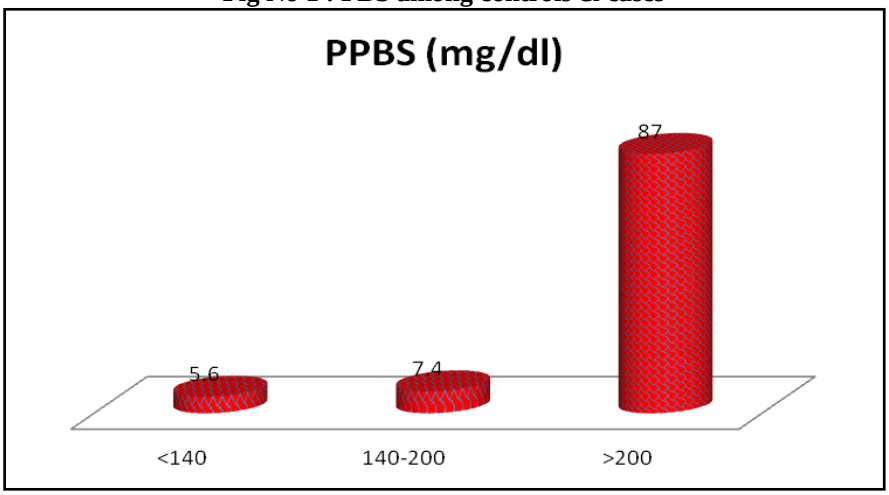

Fig No 2 : PPBS distribution among cases

SBP (mm Hg)	Cases		Controls	
	No	%	No	%
<130	8	14.8	54	100.0
>130	46	85.2	0	0.0
Total	54	100.0	54	100.0
Mean ± SD	148.26±16.83		112.96±5.64	

Table No 4 : Comparison Of SBP(mm Hg) among cases & controls

DBP (mm Hg)	Cases		Controls	
	No	%	No	%
<85	16	29.6	54	100.0
>85	38	70.4	0	0.0
Total	54	100.0	54	100.0
Mean ± SD	88.81±7.35		74.22±5.08	

Table No 5 : Comparison Of DBP(mm Hg) among cases & controls

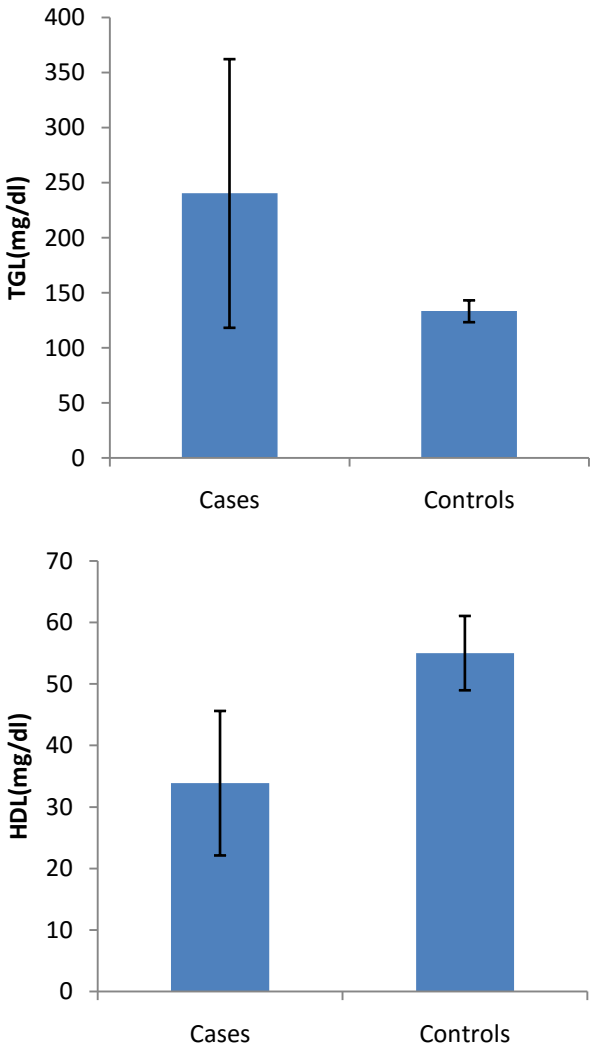

Fig No 3 : TG & HDL levels among cases & controls

TSH (mlU/ml)	Cases		Controls	
	No	%	No	%
<0.45	0	0.0	0	0.0
0.45-4.5	35	64.8	50	92.6
>4.5	19	35.2	4	7.4
Total	54	100.0	54	100.0
Mean ± SD	5.75±9.84		2.81±2.95	

Table No 6 : Comparison of TSH levels among cases & controls

Thyroid status	Cases (n=54)		Controls (n=54)	
	No	%	No	%
Euthyroid	35	64.8	50	92.6
Sub clinical hypothyroid	13	24.1	1	1.9
Hypothyroid	6	11.1	3	5.6
Inference	Hypothyroid and Subclinical hypothyroid is significantly more associated with cases with P<0.001**			

Table No 7 : Thyroid status

VARIABLES	CONTROL	METABOLIC SYNDROME
AGE (yrs)	54.13±6.16	54.87±12.68
BMI (kg/m^2)	23.12±1.21	29.77±3.17
WC (cms)	69.07±4.73	89.07±5.31
FBS (mg/dl)	80.76±9.55	187.02±59.86
SBP (mmHg)	112.96±5.64	148.26±16.83
DBP (mmHg)	74.22±5.08	88.81±7.35
TG (mg/dl)	133.35±9.93	240.35±122.01
HDL (mg/dl)	55.01±6.04	33.87±11.74
TSH (mlU/ml)	2.81±2.95	5.75±9.84

Table No 8 : Baseline characteristics of study population

IV. Discussion

The concept of Metabolic syndrome was first described in 1923 by Kylin, a Swedish physician, as a clustering of hypertension, hyperglycemia and gout as a syndrome. Subsequently, several other metabolic abnormalities have been associated with this syndrome, including obesity, microalbuminuria and abnormalities in fibrinolysis and coagulation. It is also known as insulin resistance syndrome, plurimetabolic syndrome, deadly quartet, dysmetabolic syndrome, beer belly syndrome & atherothombogenic syndrome.

There are various criteria based on certain clinical, anthropometric and biochemical parameters to define the metabolic syndrome. Commonly used are International Diabetes Federation (IDF)

The prevalence of metabolic syndrome varies around the world, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of metabolic syndrome increases with age[1].

There is high prevalence of metabolic syndrome in urban Indian subjects. Socioeconomic (high educational and occupational status) and lifestyle (high fat diet, low physical activity, overweight and obesity) factors are important. Prevalence of metabolic syndrome was significantly greater in subjects with highest vs. lowest categories of education (45 vs. 26%), occupation (46 vs. 40%), fat intake (52 vs. 45%), sedentary lifestyle (47 vs. 38%) and body mass index (66 vs. 29%) ($p < 0.05$)[3]. This has been the reason for the increased cardiovascular morbidity and mortality in the country[4].

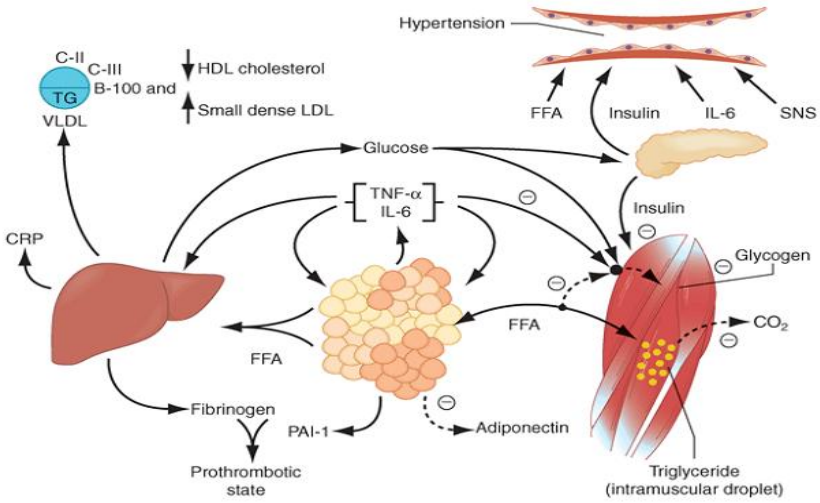

Figure No 4 : Pathophysiology Of Metabolic Syndrome

Hypothyroidism is associated with all parameters of metabolic syndrome except increase in fasting blood glucose[5]. More than 60% of hypothyroid patients have obesity, there is decrease in basal metabolic rate and energy metabolism in hypothyroidism[6]. In hypothyroidism , the hemodynamic alterations causes narrowing of pulse pressure, prolongation of circulatory time and decrease in blood flow to the tissues[7]. Systemic vascular resistance is increased and results in hypertension[8]. Rotterdam study suggested that there was a two fold increase in risk of atherosclerosis in hypothyroid patients[9]. Both the synthesis and degradation of lipids are depressed in hypothyroidism, the latter especially so, the net effect being one of the lipid accumulation, especially of LDL cholesterol and triglycerides[10]. The increase in serum cholesterol in hypothyroidism is

accompanied by increased levels of serum phospholipids, serum triglycerides and LDL cholesterol. The activity of cholesterol ester transfer protein is decreased in hypothyroidism, thus HDL cholesterol level reduced in hypothyroidism. Glucose intolerance in hypothyroidism is not proved in latest studies, though Shah et al. published insulin metabolism in hypothyroidism in 1975 indicating that glucose intolerance of the hypothyroid state is not characterized by insulin resistance . Aneemieke Ross et al. in 2007 found that free T4 was significantly associated with insulin resistance and with four of five components of the metabolic syndrome (except glucose intolerance)[11].

In our study mean systolic pressure, diastolic pressure, waist circumference, fasting blood sugar, total cholesterol, LDL cholesterol, triglycerides and TSH values were significantly higher in the metabolic syndrome group compared to the control group. These observations are similar to study by Uzunlulu et al[12]. Lai Y, Wang J, et al study of more than 1,500 subjects, found that those with metabolic syndrome had statistically significantly higher Thyroid Stimulating Hormone (TSH) levels than healthy control subjects. Subclinical hypothyroidism was also correlated with elevated triglyceride levels and increased blood pressure. Slight increases in TSH may put people at higher risk for metabolic syndrome[13]. These results are similar to our study. Research published in the February 2007 issue of the Journal of Clinical Endocrinology and Metabolism found a connection between thyroid function & metabolic syndrome. In those with normal TSH levels, the thyroid hormone level of free T4 was important. Free T4 levels that were slightly low, but still within the normal range, significantly increased the risk of many risk factors for metabolic syndrome[14]. The Tromso study and the Basel thyroid study have shown that L-Thyroxine replacement in patients with sub-clinical hypothyroidism has a beneficial effect on low density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism. An important risk reduction in cardiovascular mortality of 9–31% can be estimated from the observed improvement in low density lipoprotein cholesterol[15]. Elevated triglycerides, low HDL cholesterol and increased waist circumference were more common in women whereas increased triglycerides, low HDL cholesterol and hypertension were more common in men. Higher prevalence of metabolic syndrome in women is because of higher rate of obesity.

Comparison Of Prevalence Of Thyroid Dysfunction In Metabolic Syndrome With Other Studies

Studies	Prevalence
Ghanshyam ps shantha et al[2]	29.3 %
Chandra L et al[16]	21.1 %
Uzunula et al[12]	16.4 %
P. Gyawali et al[17]	31.25 %
Present Study	35.2%

Comparsion Of Type Of Thyroid Dysfunction With Other Studies

Studies	Euthyroid	Subclinical Hypothyroid	Hypothyroid	Subclinical hyperthyroid
Ghanshyamps shantha et al[2]	70.7 %	21.9 %	7.4 %	0%
P Gyawali et al[17]	68.75 %	28. 9 %	1.55 %	0.8 %
Present Study	64.8%	24.1%	11.1%.	0%

V. Conclusion

Thyroid dysfunction is common in metabolic syndrome patients. In our study it was found in 35.2% of metabolic syndrome patients of which 24.1% had subclinical hypothyroidism & 11.1 % had hypothyroidism. Since the prevalence of hypothyroidism (subclinical and overt) is more common in metabolic syndrome as evident from our study, early detection and thyroxine replacement could reduce the significant cardiovascular risk in these patients. However, there is still a controversy whether the patients with subclinical hypothyroidism would be benefited from thyroxine replacement. It is better to look for Thyroid dysfunction while managing metabolic syndrome patients for the effect of better outcome.List of abbreviations :BMI: Body Mass Index, FBS Fasting Blood Sugar, WC : Waist Circumference TSH : Thyroid Stimulating Hormone, TGL : Triglycerides,

HDL : High Density Lipoprotein, SBP : Systolic Blood Pressure, DBP : Diastolic Blood Pressure PPBS : Post Prandial Blood Sugar, LPL : Lipoprotein LipaseVLDL : Very Low Density Lipoprotein, PAI : Plasminogen Activator InhibitorAPO-B : Apolipoprotein B, FT4 : Free T4

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