"A CROSS-SECTIONAL STUDY TO DETERMINE THE ASSOCIATION OF INTERLEUKIN-18 WITH METABOLIC SYNDROME"

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Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

Under the Guidance of

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MAY - 2012

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ACKNOWLEDGEMENT

I take this opportunity to extend my gratitude and sincere thanks to all those who have helped me to complete this dissertation.

I am, extremely indebted and grateful to my guide, **Dr. ARATHI DARSHAN MD,** Professor, Department of Medicine, for her constant guidance and encouragement, in preparing this dissertation and during my post-graduate training period.

It gives me immense pleasure to express my deep sense of gratitude to my Professor and Head, Department of Medicine **Dr. V. A. KOTHIWALE MD, Ph.D,** for his excellent guidance, encouragement and constant inspiration during my course.

My sincere thanks and gratitude to Emeritus professor **Dr. H. B. RAJASHEKHAR MD,** who has been a constant source of inspiration.

It gives me great pleasure to express my gratitude and sincere thanks to **Dr. V. G. SOMANNAVAR MD, Dr. REKHA S. PATIL, MD, Dr. B. SRINIVAS, MD, Dr. PRAKASH BABALICHE, MD, Dr. RAJU BADIGER MD**, for their guidance and encouragement during my postgraduate course.

I am very much thankful to **Dr. NAVEEN ANGADI MD, Dr. JAYAPRAKASH APPAJIGOL MD,** for their encouragement and advice.

I extend my sincere thanks to my Post-graduate Colleagues **DR. RANJAN MODI, DR. HEMANTH KUMAR, DR. TOBY**

CHANDY, DR. SNEHA SIRDESHPANDE, DR. CHANDRAMOULI REDDY, DR. VEENA S., DR. P. SASANKA, DR VIKAS PATIL, DR. YESHWANTH G, DR. GAURAV SUBHEDAR, DR SALIL PATKAR and **DR. NAVEEN CHARANTHIMATH** who have helped me in preparing this dissertation.

I extend my sincere appreciation to the Biochemistry department for helping me with the necessary investigations, without which, this dissertation would not have been possible.

I would like to take this opportunity to thank my parents, **DR. YOGISH B. RAO** and **DR. MEDHA Y. RAO**, my brother, **DR ROHEET B. RAO**, for their unyielding support and guidance.

Last, but not the least, my heartfelt thanks to all **PATIENTS** who formed this study group and co-operated wholeheartedly.

I thank the Almighty for providing me with this opportunity and the resources to bring it to completion.

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LIST OF ABBREVIATIONS USED

%	– Percentage
ACE	– Angiotensin converting enzyme
AHA	– American Heart Association
Apo B	– Apolipoprotein B
Asp35	– Aspartate35
AT II	– Angiotensin II
ATP III	– adult treatment panel III
BMI	– Body mass index
BP	– Blood pressure
CAD	– Coronary Artery Disease
CHD	– Coronary heart disease
cms	– Centimeters
CRP	– C-reactive protein
CVD	– Cardiovascular Disease
DM	– Diabetes Mellitus
FBS	– Fasting blood glucose
FFA	– Free Fatty acids
FPG	– Fasting plasma glucose
HDL	– High density Lipoprotein
HDL-C	– High density Lipoprotein Cholesterol
HIV	– Human Immunodeficiency Virus
hsCRP	– Highly sensitive C-Reactive protein
HTN	– Hypertension
ICAM-1	– Intracellular adhesion molecule-1

ICE – Interleukin 1β converting enzyme

IDF – International Diabetes Federation

IFG – Impaired fasting glucose

IFN-γ – Interferon γ

IGT – Impaired glucose tolerance

IL-1 – Interleukin 1

IL-18 – Interleukin 18

IL-18 BP – Interleukin 18 binding protein

IL-6 – Interleukin 6

kD – kilodalton

kg/m^2 – Kilograms per square metre

LPL – Lipoprotein Lipase

MetS – Metabolic syndrome

mg – milligrams

mg/dL – Milligrams per deciliter

MI – Myocardial Infarction

min – Minute

mm Hg – Millimeters of mercury

mMol/L – Millimoles per litre

MMP – Matrix metalloproteinase

NAFLD – Non-alcoholic fatty liver disease

NCEP – National cholesterol education programme

NHLBI – National Heart, Lung, and Blood Institute

NO – Nitric oxide

OGTT – Oral glucose tolerance test

OSA	– Obstructive sleep apnoea syndrome
PCOS	– Polycystic ovarian syndrome
SD	– standard deviation
TG	– Triglycerides
Th0	– T-helper cell 0
Th1	- T-helper cell 1
Th2	- T-helper cell 2
TNF-α	– Tumor necrosis factor – α
TZD	– Thiazolidinediones
U.S.	– United states
VCAM-1	– Vascular cell adhesion molecule 1
VLDL	– Very low density lipoprotein
WHO	– World Health Organization
μg/min	– Microgram per minute
μU/L	– microunit per litre

ABSTRACT

Background and objectives

The metabolic syndrome (MetS) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. Interleukin-18 (IL-18), a recently described member of the IL-1 cytokine superfamily, is now recognized as an important regulator of innate and acquired immune responses. The present study was undertaken to study the association of IL-18 with metabolic syndrome and to correlate IL-18 levels with the different components of metabolic syndrome as well as its complications.

Methodology

The present one year cross sectional study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients of metabolic syndrome based on IDF criteria specific for south Asians during the period of January 2010 to December 2010. Estimation of IL-18 was done using standard recombinant IL-18 enzyme linked immuno sorbent assay (ELISA) kit. Interleukin-18 levels above 216 pg/mL were considered as abnormal.

Results

Males accounted for 64%. The mean age for the study population was 60.30 ± 9.43 years. Diabetes accounted for 71% as past history. 53% subjects were in the pre-obese group with a BMI between 25 to 29.99 kg/m^2. All the patients (100%) had abnormal WC. The mean fasting blood sugar level were 142 ± 28.8 mg/dL. 71 patients were found to have an elevated Il-18 level (71%)

whereas 29 subjects had a IL-18 ≤ 215. Of the 100 patients studied, 64% had three components, 29% had four and 7% had all five components of the metabolic syndrome. The strongest correlation of IL-18 was observed with HOMA-IR with a correlation coefficient of 0.646 ($p \leq 0.001$).

Interpretation and conclusion

Interleukin levels were found to be significantly higher in patients with metabolic syndrome. The findings of this study indicate a utility of IL-18 as a prognostic marker in patients with metabolic syndrome.

Keywords

Interleukin-18; Lipid profile; Metabolic syndrome;

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Chapter 1

Introduction

INTRODUCTION

The metabolic syndrome is a cluster of risk factors for cardiovascular disease (CVD), including obesity, hypertension, elevated triglycerides and low levels of HDL Cholesterol.

Metabolic syndrome is a burgeoning global problem. Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America.[1] MetS is also considered an emerging epidemic in developing East Asian countries including China, Japan, and Korea. The prevalence of metabolic syndrome may range from 8-13% in men and 2-18% in women depending on the population and definitions used.[2-4] In Japan, the Ministry of Health, Labor, and Welfare has instituted a screening and interventional program.[5] Metabolic syndrome has been recognized as a highly prevalent problem in many other countries worldwide.[6-11]

The clinical manifestations of this syndrome may include hypertension, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and abdominal obesity.

Abundant data suggest that patients meeting these diagnostic criteria have a greater risk of having significant clinical consequences, the two most prominent and dreaded of which are the development of coronary heart disease[12] and diabetes mellitus (DM).[13] It also increases risk of stroke, fatty liver disease, and several cancers.[14]

Initial laboratory studies in patients suspected of having metabolic syndrome include standard biochemical parameters to assess for hyperglycemia, renal dysfunction and lipid studies to assess for hypertriglyceridemia or low HDL levels.

Obesity and insulin resistance are considered central to the pathophysiology of this metabolic and cardiovascular syndrome.[15,16] Recently, activated innate immunity and chronic inflammation have also been causally implicated and may represent a potential link between metabolic syndrome, diabetes, and atherosclerosis.[17-19]

Interleukin-18 (IL-18), a recently described member of the IL-1 cytokine superfamily, is now recognized as an important regulator of innate and acquired immune responses. IL-18 is expressed at sites of chronic inflammation, in autoimmune diseases, in a variety of cancers, and in the context of numerous infectious diseases. Recent evidence suggests that IL-18 may serve as a biomarker of cardiovascular risk. IL-18 levels increase in patients with stable and unstable angina and in those with myocardial infarction (MI).

The proinflammatory state, that accompanies the metabolic syndrome associates with both insulin resistance and endothelial dysfunction; provides a connection between inflammation and metabolic processes which is highly deleterious for vascular functions. IL-18, participates in the formation, progression, and vulnerability of atherosclerotic plaque.

Inflammatory markers including CRP, IL-6, and IL-18 add prognostic information regarding cardiovascular mortality in subjects with known coronary

artery disease and metabolic syndrome. But only IL-18 has been identified as an independent predictor in multivariate analyses. IL-18 strongly predicted cardiovascular events in subjects with metabolic syndrome, and the prediction was even more pronounced in the sole presence of elevated fasting glucose.[20]

Even in the face of compelling evidence in favour of this theory, there are very few studies done in this area especially in India. Hence, the present study was undertaken to study the association of IL-18 with metabolic syndrome and to correlate IL-18 levels with the different components of metabolic syndrome as well as its complications.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

1. To study the association of IL-18 with metabolic syndrome.
2. To correlate IL-18 levels with the different components of metabolic syndrome as well as its complications.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

"Four in five deaths from Non Communicable Diseases now occur in low- and middle- income countries. Without decisive action, the Non Communicable Disease burden threatens to undermine the benefits of improving standards of living, education and economic growth in many countries"

- MARTIN SILINK

President, International Diabetes Federation

Most of the developing countries including India are undergoing an epidemiological transition. Infectious and nutritional diseases are receding among adults while non communicable diseases are becoming increasingly common, as the cause of morbidity and mortality. Demographic projections indicate a major increase in cardiovascular disease mortality in India due to increase in life expectancy and change in the age structure of the growing population.[21]

Non-communicable or chronic diseases are diseases of long duration and generally slow in progression such as heart disease, stroke, cancer, chronic respiratory diseases, hypertension and diabetes. These diseases are now the leading cause of mortality in the world, representing 63% of all deaths. Out of the 36 million people who died from chronic disease in 2008, nine million were under 60 and ninety per cent of these premature deaths occurred in low- and middle-income countries.[22]

The hallmark of management of Non-communicable diseases is Primary and Secondary prevention. The essence of prevention lies in risk factor identification and reduction. Metabolic syndrome has emerged as an important constellation of risk factors that has been shown to effectively predict the development of Type II Diabetes Mellitus and Cardiovascular Disease.[12,13]

The 'Metabolic Syndrome' is a widely prevalent and multi-factorial disorder that presents in a distinct, albeit heterogenous phenotype.[23]

Although obesity and insulin resistance are not synonymous with the metabolic syndrome, they are integral features in this derangement of adipocyte physiology and carbohydrate metabolism.[23]

Metabolic syndrome was initially observed in 1923 by Kyln, who described the clustering of hypertension, hyperglycemia and gout as the syndrome. Subsequently, several other metabolic abnormalities have been associated with this syndrome, including obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation.[24]

In 1988, Gerald Reaven reintroduced the concept of Syndrome X for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides and low HDL concentration.[15]

The syndrome has been given several names, including the 'metabolic syndrome', the 'insulin resistance syndrome', the 'plurimetabolic syndrome', and the 'deadly quartet'.[24]

In 1998, WHO proposed a unifying definition for the syndrome and chose to call it the 'metabolic syndrome' rather than the 'insulin resistance syndrome'.[25]

This name was chosen primarily because it was the cause of all the components of the syndrome.

The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) included clinical diagnosis guidelines for the Metabolic Syndrome. Compared with findings from earlier studies and WHO guidelines, the new ATP III defines criteria which can be measured in clinical practice.[23]

The metabolic syndrome (MetS) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function.[26] It is a risk factor for coronary heart disease (CHD), as well as diabetes, fatty liver and several cancers. The clinical consequences of this syndrome may include hypertension, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C) and abdominal obesity.

Diagnosis

Under recent guidelines, revised in 2005 by the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA),[27] metabolic syndrome is diagnosed when a patient has at least three of the following five conditions:

1. Fasting glucose $\geq$ 100 mg/dL (or receiving drug therapy for hyperglycemia)

2. Blood pressure ≥ 130/85 mm Hg (or receiving drug therapy for hypertension)
3. Triglycerides ≥ 150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
4. HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
5. Waist circumference ≥ 102 cm (40 in) in men or ≥ 88 cm (35 in) in women; if Asian American, ≥ 90 cm in men (35 in) or ≥ 80 cm in women (32 in)

Other Definitions of Metabolic syndrome:[25,28,29]

	WHO 19996[25]	**EGIR 1999**[28]	**NCEP ATP III 2001**[29]
	Glucose intolerance, IGT or diabetes and /or insulin resistance together with two or more of the following	Insulin resistance (Defined as hyperinsulinemia – Top 25% of fasting insulin values among the non diabetic population) plus two of the following	Three or more of the following five risk factors
Fasting plasma glucose	≥ 140 / 90 mm Hg	≥ 6.1 mmol/L (110 mg/dL) but non diabetic	≥ 5.6 mmol/L 100 mg/dL
Blood pressure triglycerides	Raised plasma triglycerides ≥ 1.7 mmol/L (150 mg/dL) and / or	≥ 140/90 mm Hg or treatment	≥ 130 /≥ 85 mm Hg 1.7 mmol/L (150 mg/dL)
HDL cholesterol	Men < 0.9 mmol/L (39 mg/dL)	≥ 2.00 mmol/L (178 mg/dL0 or treatment and/or < 1.0 mmol/L (39 mg/dL) or treatment	Men <1.03 mmol/L (40 mg/dL) Women: < 1,29 mmol/L (< 50 mg/dL)
Obesity	Men WC ratio > 0.90	Men: WC ≥ 94 Cms	Men WC > 102 Cm
	Women WC ratio > 0.85 And/or BMI > 30 Kg/m2	Women: WC ≥ 80 Cms	Women WC > 88 Cms
Microalbuminuria	Urinary albumin excretion rate ≥ 20 µg/min or albuminacreatiine ratio ≥ 30 mg/g		

In 2005, the International Diabetes Federation (IDF) published its definition of the metabolic syndrome in adults. The intention was to rationalize the existing multiple definitions of the syndrome and to have a single, universally accepted diagnostic tool that is easy to use in clinical practice and that does not rely upon measurements only available in research settings.[30]

IDF criteria for the diagnosis of metabolic syndrome[30]

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

- Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups)

  Plus any two of the following four factors:

- Raised TG level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If FBS is above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Country /Ethnic group		Waist circumference
Europids: In USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cms
	Female	≥ 80 cms
South Asians: Based on Chinese, Malay and Asian Indian population	Male	≥ 90 cms
	Female	≥ 80 cms
Chinese	Male	≥ 90 cms
	Female	≥ 80 cms
Japanese	Male	≥ 90 cms
	Female	≥ 80 cms
Ethnic South and Central Americans	Use South Asian recommendation until more specific data are available	
Sub Saharan Africans	Use European data until more data are available	
Eastern Mediterranean and middle east (Arab) populations	Use European data until more data are available	

Abundant data suggests, that patients meeting these diagnostic criteria have a greater risk of having significant clinical consequences, the 2 most prominent and dreaded of which are the development of diabetes mellitus (DM) and coronary heart disease. In addition, pooled data from 37 studies involving more than 170,000 patients have shown that metabolic syndrome doubles the risk of coronary artery disease.[1] It also increases risk of stroke, fatty liver disease, diabetes[12] and cancer.[13]

Epidemiology

Frequency

Metabolic syndrome is increasing in prevalence, paralleling an increasing epidemic of obesity. In the United States, data from a 1999-2000 survey showed that the age-adjusted prevalence of metabolic syndrome among adults aged 20 years or older had risen from 27% (data from 1988-1994) to 32%.[31]

Metabolic syndrome is a burgeoning global problem. Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America.[27] It is also considered an emerging epidemic in developing East Asian countries including China, Japan, and Korea, the prevalence of metabolic syndrome may range from 8-13% in men and 2-18% in women depending on the population and definitions used.[2,3,4] Metabolic syndrome has been recognized as a highly prevalent problem in many other countries worldwide.[6-10,32] In a recent study done on Indian urban population, Metabolic syndrome was present in 31.6%; prevalence was 122 (22.9%) in men and 223 (39.9%) in women.[9]

With the formulation of NCEP/ATP III guidelines, some uniformity and standardization has occurred in the definition of metabolic syndrome and has been very useful for epidemiological purposes. At present, metabolic syndrome is an all or none diagnosis.[33]

The prevalence of the metabolic syndrome depends on age, ethnic background, and gender. It rises linearly from 20 to 50 years and plateaus

thereafter. Looking at various studies around the world, which included population samples, aged from 20 to 25 and upwards, the prevalence varies from 8% (India) to 24% (United States) in men and from 7% (France) to 46% (India) in women.[34] Two Indian studies, which differed in their definition of obesity: the first[35] used the obesity criteria suitable for Indians, while the second[36] used the standard ATP III definition of obesity. Both studies used population based samples within the age range but reported prevalence of 13% in Jaipur[36] and 41% in Chennai.[35] Although, the prevalence of obesity in the two study groups was quite similar (31% versus 33%), despite the different definitions used, far larger differences were observed between the two studies for the prevalence of elevated triglycerides (46% vs. 30%), hypertension (55% vs. 39%) and elevated fasting plasma glucose (27% vs. 5%); indicating a far larger impact of these risk factors than obesity alone.

Various Factors contributing to increasing prevalence of metabolic syndrome have been identified:

1. Atherogenic dyslipidemia, Elevated Triglycerides, apolipoprotein B and small low-density lipoprotein, low HDL.
2. Elevated plasma glucose.
3. Elevated blood pressure.
4. Pro-thrombotic state.
5. Pro-inflammatory state

Many studies[37,38,39] have reported that low socio-economic status is associated with a higher mortality rate due to cardiovascular disease. A low

education level links cardiovascular disease with risk factors such as smoking, hypertension, impaired glucose tolerance, diabetes mellitus, physical inactivity and overweight associated with other metabolic abnormalities.

Age

The prevalence of metabolic syndrome increases with age, with about 40% of people older than 60 years meeting the criteria.[31] The metabolic syndrome affects 44% of the U.S. population older than age 50. A greater percentage of women older than age 50 have the syndrome than men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

However, metabolic syndrome can no longer be considered a disease of only adult populations. Alarmingly, metabolic syndrome and diabetes mellitus are increasingly prevalent in the pediatric population, again in parallel with a rise in obesity.[40] In the United States, children are becoming obese at triple the rate compared with the 1960s, making the study and treatment of this problem vital. The epidemic of metabolic syndrome in children and adolescents is an international phenomenon, which lead the International Diabetes Foundation to publish an updated consensus statement to guide diagnosis and further study of the condition.[41,42]

Aetiopathogenesis

Risk factors

Overweight/Obesity

Central adiposity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are normal weight may also be insulin-resistant and have the syndrome.

Sedentary Lifestyle

Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol; and a trend toward increased triglycerides, blood pressure, and glucose intolerance in the genetically susceptible.

Diabetes Mellitus

DM is included in both the NCEP and International Diabetes Foundation (IDF) definitions of the metabolic syndrome. It is estimated that the large majority (~75%) of patients with type 2 diabetes or impaired glucose tolerance (IGT) have the metabolic syndrome. The presence of the metabolic syndrome in these populations relates to a higher prevalence of CVD compared to patients with type 2 diabetes or IGT without the syndrome.

Coronary Heart Disease

The approximate prevalence of the metabolic syndrome in patients with coronary heart disease (CHD) is 50%, with a prevalence of 37% in patients with premature coronary artery disease.

Lipodystrophy

Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic (Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (HIV-related lipodystrophy in patients treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of the metabolic syndrome's components.

Risk factors occur in isolation only 30% of the time, and clustering of three or more factors occurs 17% of the time in both genders. Clustering of the factors was related to baseline obesity and weight gain during adulthood.[43]

In Framingham and in other observational studies, the central core of metabolic risk factors were found to be highly related, including triglycerides, HDL-C, BMI, waist circumference, or fasting insulin levels, to insulin levels after an oral glucose challenge test. In addition to a central metabolic syndrome core, there has been a hypertension cluster with shared variance components that included BMI, systolic pressure and diastolic pressure.[43]

Pathogenesis

Metabolic syndrome is a heterogeneous condition characterized by visceral adiposity, dyslipidemia, hypertension, and insulin resistance. The metabolic syndrome with its clustering of metabolic and atherosclerotic risk factors is a strong determinant of type 2 diabetes and cardiovascular disease (CVD). Obesity and insulin resistance are considered central to the pathophysiology of this metabolic and cardiovascular syndrome.[20,44]

Insulin resistance

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by an incompletely understood defect in insulin action. The mechanisms underlying the metabolic syndrome are not fully known; however resistance to insulin stimulated glucose uptake seems to modify biochemical responses in a way that predisposes to metabolic risk factors.[34]

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids which are derived predominantly from adipose tissue triglyceride stores released by hormone-sensitive lipase. Fatty acids are also derived through the lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase (LPL). Insulin mediates both antilipolysis and the stimulation of LPL in adipose tissue. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids

impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation are seen in liver.

Both adipose cell enlargement and infiltration of macrophages into adipose tissue result in the release of proinflammatory cytokines and promote insulin resistance. Insulin resistance appears to be the primary mediator of metabolic syndrome.[45] Insulin promotes glucose uptake in muscle, fat, and liver cells, and can influence lipolysis and production of glucose by hepatocytes. Additional contributors to insulin resistance include abnormalities in insulin secretion and insulin receptor signaling, impaired glucose disposal, and proinflammatory cytokines. These abnormalities, in turn, may result from obesity with related increases in free fatty acid levels and changes in insulin distribution (insulin accumulates in fat).

The distribution of adipose tissue appears to affect its role in metabolic syndrome. Fat that is visceral or intra-abdominal correlates with inflammation whereas subcutaneous fat does not.[46] Abdominal fat is known to produce potentially harmful levels of cytokines, such as tumor necrosis factor, adiponectin, leptin, resistin, and plasminogen activator inhibitor.[47]

Dyslipidemia

In general, FFA flux to the liver is associated with increased production of apoB–containing, triglyceride-rich very low density lipoproteins (VLDLs). The effect of insulin on this process is complex, but *hypertriglyceridemia* is an excellent marker of the insulin-resistant condition.

The other major lipoprotein disturbance in the metabolic syndrome is a *reduction in HDL cholesterol*. This reduction is a consequence of changes in HDL composition and metabolism which results in an increased clearance of HDL from the circulation.

In addition to HDL, LDLs are also modified in composition. With fasting serum triglycerides >2.0 mM (~180 mg/dL), there is almost always a predominance of small dense LDLs. Small dense LDLs are thought to be more atherogenic. They may be toxic to the endothelium and also have increased susceptibility to oxidation and are selectively bound to scavenger receptors on monocyte-derived macrophages.

Glucose Intolerance

The defects in insulin action lead to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues, i.e., muscle and adipose tissue. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycemia. Ultimately, this compensatory mechanism fails, usually because of defects in insulin secretion, resulting in progress from IFG and/or IGT to DM.

Hypertension

The relationship between insulin resistance and hypertension is well established. In the setting of insulin resistance, the vasodilatory effect of insulin is lost, but the renal effect on sodium reabsorption is preserved. Insulin also

increases the activity of the sympathetic nervous system, an effect that may also be preserved in the setting of the insulin resistance. Finally, insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol 3-kinase signaling which may cause an imbalance between the production of nitric oxide and secretion of endothelin-1, leading to decreased blood flow.

Role of Inflammation

Abundant in vitro and in vivo data implicate inflammation in atherogenesis, leading to the current understanding of atherosclerosis as a chronic inflammatory disease. Recent evidence demonstrates that a complex network of cytokines orchestrates the underlying immunologic and inflammatory processes.[49]

A central role has been attributed to the pro-inflammatory cytokines, tumor necrosis factor a (TNF- α) and interleukin (IL)-6, supported by the fact that both are produced in substantial amounts by human adipose tissue. TNF- α impairs insulin-stimulated glucose uptake in a variety of cells and decreases lipoprotein lipase activity. Both cytokines increase hepatic lipogensis and elicit a systemic acute- phase response.[34]

Furthermore, various aspects of the acute-phase response, such as fibrinogen and plasminogen activator inhibitor-1 levels, whole-blood viscosity, and white blood cell count, have recently been found to correlate positively with the metabolic syndrome. This is of particular interest because inflammation plays an important role in the pathogenesis of atherothrombosis.[34]

Moreover, C-reactive protein (CRP), the classic and exquisitively sensitive acute phase reactant, shows a strong independent association with the risk of Coronary Heart Disease and other atherothrombotic events. CRP levels have also been found to correlate with BMI and some features of the metabolic syndrome.[49]

Clinical Relevance

The clinical relevance of the metabolic syndrome is related to its role in the development of cardiovascular disease. Two recent prospective population-based studies confirmed that the metabolic syndrome identified a high-risk group of persons who would have been missed by only consideration of the conventional risk factors. The incidence of coronary disease along with carotid atherosclerosis is higher in patients with metabolic syndrome along with higher mortality from all such causes.[34]

Although for many obese patients the risk of developing metabolic syndrome is quiet evident, but studies[34] also show that the risk of having the metabolic syndrome increases steeply even within the overweight or the "preobese" range. Detecting these overweight individuals and the 6% of normal weight individuals with the metabolic syndrome and implementing preventive lifestyle interventions-diet education, physical activity, weight control, smoking cessation, and related behavior modification- is of a high clinical priority.

Other Associated Conditions

In addition to the features specifically associated with metabolic syndrome, insulin resistance is accompanied by other metabolic alterations

Nonalcoholic Fatty Liver Disease

Fatty liver is relatively common. However, in NASH, both triglyceride accumulation and inflammation coexist.

Hyperuricemia

Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid, whereas the increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, relates to endothelial dysfunction. Microalbuminuria may also be caused by altered endothelial pathophysiology in the insulin-resistant state.

Polycystic Ovary Syndrome

PCOS is highly associated with the metabolic syndrome, with a prevalence between 40 and 50%. Women with PCOS are 2–4 times more likely to have the metabolic syndrome compared to women without PCOS.

Obstructive Sleep Apnea

OSA is commonly associated with obesity, hypertension, increased circulating cytokines, IGT, and insulin resistance.

Presentation

History

As with other diseases, careful history taking is important in metabolic syndrome. Even though the condition is diagnosed based on physical and laboratory features, it may be suspected if symptoms of any of the component disorders are present, such as the increased hunger, thirst, or urination that may accompany hyperglycemia. Patients reporting a history of hypertension, dyslipidemia warrant screening for metabolic syndrome. Symptoms suggesting the rise of cardiovascular and other complications, such as chest pain or shortness of breath, must be investigated carefully. As lifestyle changes can ameliorate the condition, attention should be paid to the patient's dietary habits and exercise routines so that areas for improvement can be identified.

The social history is important for identifying additional risks, such as tobacco use, which may exacerbate the increased cardiovascular complications associated with metabolic syndrome. A family history should be obtained because genetics may play an important role in metabolic syndrome. This feature of the disease is under active investigation; however, currently no gene or group of genes has been implicated consistently, suggesting that the environment exerts substantial influence.[50] Finally, a thorough review of systems may help identify related problems, such as menstrual irregularities that can be seen in polycystic ovarian syndrome.

Physical

The physical examination is crucial in patients with metabolic syndrome as the findings of elevated blood pressure and abdominal obesity are 2 of the 5 diagnostic criteria. Measurement and documentation of waist circumference are important routines when screening for metabolic syndrome. Additionally, the examination may reveal findings reflective of the other criteria. For example, patients with insulin resistance and hyperglycemia or diabetes mellitus may have acanthosis nigricans, hirsutism, peripheral neuropathy, and retinopathy. Patients with severe dyslipidemia may have xanthomas or xanthelasmas. The presence of arterial bruits may portend a higher risk of cardiovascular complications.

Laboratory Studies

Fasting lipids and glucose are needed to determine if the metabolic syndrome is present. The measurement of additional biomarkers associated with insulin resistance must be individualized. Such tests might include apo B, high-sensitivity CRP, fibrinogen, uric acid, urinary microalbumin, and liver function tests. A sleep study should be performed if symptoms of OSA are present. If PCOS is suspected based on clinical features and anovulation, testosterone, luteinizing hormone, and follicle-stimulating hormone should be measured.

The Metabolic Syndrome: Treatment

Lifestyle

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to the disorder. With weight reduction, the

improvement in insulin sensitivity is often accompanied by favorable modifications in many components of the metabolic syndrome. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. The tendency for weight regain after successful weight reduction underscores the need for long-lasting behavioral changes.

Diet

Before prescribing a weight-loss diet, it is important to emphasize that it takes a long time for a patient to achieve an expanded fat mass; thus, the correction need not occur quickly. Diets restricted in carbohydrate typically provide a rapid initial weight loss. However, after one year, the amount of weight reduction is usually unchanged. Thus, adherence to the diet is more important than which diet is chosen. Diets restricted in saturated fats (<7% of calories), trans fat (as few as possible), and cholesterol (<200 mg daily) should be applied aggressively.

Physical Activity

Before a physical activity recommendation is provided to patients with the metabolic syndrome, it is important to ensure that this increased activity does not incur risk.For the inactive participant, gradual increases in physical activity should be encouraged to enhance adherence and to avoid injury. Although increases in physical activity can lead to modest weight reduction, 60–90 min of daily activity is required to achieve this goal. Even if an overweight or obese

adult is unable to achieve this level of activity, they still derive a significant health benefit from at least 30 min of moderate intensity daily activity.

Obesity

In some patients with the metabolic syndrome, treatment options need to extend beyond lifestyle intervention. Weight-loss drugs come in two major classes: appetite suppressants and absorption inhibitors. Appetite suppressants approved by the Food and Drug Administration include phentermine (for short-term use only, 3 months) and sibutramine. Orlistat inhibits fat absorption by ~30% and has been shown to reduce the incidence of type 2 diabetes, an effect that was especially evident in patients with baseline IGT.

Bariatric surgery is an option for patients with the metabolic syndrome who have a body mass index (BMI) of >40 kg/m^2 or >35 kg/m^2 with comorbidities.

Pharmacologic therapy:

Statins (HMG-CoA reductase inhibitors), which produce a 20–60% lowering of LDL cholesterol, are generally the first choice for medication intervention. Side effects are rare and include an increase in hepatic transaminases and/or myopathy.

The cholesterol absorption inhibitor ezetimibe is well tolerated and should be the second choice. Ezetimibe typically reduces LDL cholesterol by 15–20%. The bile acid sequestrants cholestyramine and colestipol are more effective than ezetimibe but must be used with caution in patients with the metabolic syndrome

because they often increase triglycerides. Side effects include gastrointestinal symptoms (palatability, bloating, belching, constipation, anal irritation). Nicotinic acid has modest LDL cholesterol–lowering capabilities (<20%). Fibrates are best employed to lower LDL cholesterol when both LDL cholesterol and nontriglycerides are elevated. Fenofibrate may be more effective than gemfibrozil in this group.

Triglycerides

In general, the response of fasting triglycerides relates to the amount of weight reduction achieved. A weight reduction of >10% is necessary to lower fasting triglycerides.

A fibrate (gemfibrozil or fenofibrate) is the drug of choice to lower fasting triglycerides and typically achieve a 35–50% reduction. Although several additional clinical trials have been performed, these have not shown clear evidence that fibrates reduce CVD risk as a consequence of triglyceride lowering.

Other drugs that lower triglycerides include statins, nicotinic acid, and high doses of omega-3 fatty acids.

HDL Cholesterol

Beyond weight reduction, there are very few lipid-modifying compounds that increase HDL cholesterol. Statins, fibrates, and bile acid sequestrants have modest effects (5–10%), and there is no effect on HDL cholesterol with ezetimibe or omega-3 fatty acids. Nicotinic acid is the only currently available drug with predictable HDL cholesterol-raising properties.

Blood Pressure

In patients with the metabolic syndrome without diabetes, the best choice for the first antihypertensive should usually be an ACE inhibitor or an angiotensin II receptor blocker, as these two classes of drugs appear to reduce the incidence of new-onset type 2 diabetes. In all patients with hypertension, a sodium-restricted diet enriched in fruits and vegetables and low-fat dairy products should be advocated.

Impaired Fasting Glucose

In patients with the metabolic syndrome and type 2 diabetes, aggressive glycemic control may favorably modify fasting triglycerides and/or HDL cholesterol. In those patients with IFG without a diagnosis of diabetes, a lifestyle intervention that includes weight reduction, dietary fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes. Metformin has also been shown to reduce the incidence of diabetes, although the effect was less than that seen with lifestyle intervention.

Insulin Resistance

Several drug classes [biguanides, thiazolidinediones (TZDs)] increase insulin sensitivity. Both metformin and TZDs enhance insulin action in the liver and suppress endogenous glucose production. TZDs, but not metformin, also improve insulin-mediated glucose uptake in muscle and adipose tissue. Benefits of both drugs have also been seen in patients with NAFLD and PCOS, and they

have been shown to reduce markers of inflammation and small dense LDL. In general, the beneficial effects of TZDs appear superior to those of metformin.

INTERLEUKIN-18 (IL-18)

Interleukin-18 a recently described member of the IL-1 cytokine superfamily, is now recognized as an important regulator of innate and acquired immune responses. IL-18 is expressed at sites of chronic inflammation, in autoimmune diseases, in a variety of cancers, and in the context of numerous infectious diseases.[51]

The cytokine is produced constitutively in many different cell types, including macrophages, endothelial cells, vascular smooth muscle cells, dendritic cells and Kupffer cells. IL-18 is also produced in adipocytes, but non-adipocyte cells have been identified as the main source of IL-18. In adipose tissue, IL-18 is produced as a 24-kD inactive precursor lacking a signal peptide (pro-IL-18). Pro-IL-18 is cleaved after Asp35 by the endoprotease IL-1β-converting enzyme (ICE; caspase-1) to generate a biologically active, mature 18-kD moiety.[51]

Once secreted, IL-18 is bound and inactivated by IL-18 binding protein, which is enhanced as a negative feedback mechanism in response to increased IL-18 production, ensuring protection from tissue damage due to uncontrolled proinflammatory activity.[51] IL-18 binds to its receptor, consisting of an α chain which is responsible for extracellular binding of IL-18, and a β chain which is responsible for intracellular signal transduction.[51] Although both free and protein-bound IL-18 may bind to the α chain, only the free fraction is able to activate the β chain.[51]

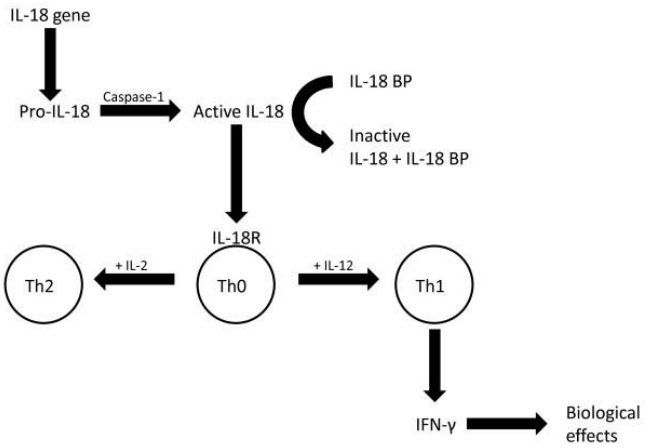


Figure 1. Regulation and biological effects of interleukin-18

Biological effects of IL 18

Although originally identified as a factor capable of inducing IFN-γ production by murine splenocytes, the effector role of IL-18 is rapidly expanding.[52]

IL-18 is a potent proinflammatory cytokine which enhances T cell and natural killer cell maturation, as well as the production of cytokines, chemokines and cell adhesion molecules. IL-18 can promote Th1 or Th2 lineage maturation dependent on underlying genetic influences and the ambient cytokine milieu. IL-18 promotes neutrophil activation, reactive oxygen intermediate synthesis, cytokine release, and degranulation.

Recent studies[53] suggest that IL-18 up-regulates intracellular adhesion molecule-1 (ICAM-1) and VCAM-1 expression on endothelial cells and synovial fibroblasts. IL-18 is particularly effective during the clearance of intracellular bacteria, fungi, and protozoa, requiring the induction of host-derived IFN-γ, which in turn evokes effector pathways involving molecules such as nitric oxide

(NO). IL-18 also plays a part in the clearance of viruses, partly through the induction of cytotoxic T cells. IL–18 may act synergistically with IL-12 to stimulate a Th1 response with production of IFN-γ, a central feature in the atherosclerotic lesion.[51]

IL 18 and Atherosclerosis

Several lines of evidence support a pro-atherogenic role for IL-18. Expression of IL-18 and the IL-18 receptor subunits are increased in atherosclerotic arteries compared with normal arterial segments. Stimulation of cell types found in atheromata with IL-18 induces proinflammatory cytokines such as interferon (IFN)-γ and IL-6, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), and enzymes capable of degrading extracellular matrix metalloproteinase(MMPs). In addition, studies in mice demonstrate that lack of IL-18 or inhibition of IL-18 signaling decreases atherosclerotic plaque formation, whereas administration of exogenous IL-18 promotes atherogenesis and yields more fatty than fibrous lesions.[48]

Interleukin-18 in the metabolic syndrome and type 2 diabetes

IL-18 has in several studies been associated with obesity, insulin resistance, hypertension and dyslipidemia. Furthermore, IL-18 has been shown to be elevated in subjects with the metabolic syndrome and to increase in parallel with an increasing number of components of the syndrome.[53]

In a large cross sectional study,[20] elevated IL-18 levels were associated with increasing number of components even after adjustment for insulin resistance, obesity, IL-6 and CRP.

Polymorphisms in the IL-18 gene have been shown to be associated with circulating IL-18 levels.[53] Interestingly, a recent study[55] showed that one such polymorphism was associated with increased serum levels of IL-18, impaired insulin sensitivity and increased risk of having the metabolic syndrome, suggesting that IL-18 might be involved in the pathogenesis of the syndrome. Therefore, IL-18 levels has been shown to correlate significantly with components of the metabolic syndrome.

IL-18 has also consistently shown strong correlations with measures of insulin resistance, including HOMA-IR and glucose levels. Circulating levels of IL-18 have consistently been reported to be elevated in patients with type 2 diabetes mellitus in cross sectional studies,[56,57,58] and have also been suggested to contribute to microangiopathy such as nephropathy in type 2 diabetes.[59]

Moreover, in two prospective cohorts,[60,61] elevated levels of IL-18 have been shown to predict the development of type 2 diabetes.

IL-18 has been proved to be even more predictive in the presence of elevated glucose, and as most subjects with metabolic syndrome had impaired fasting glucose or diabetes, it is likely that the predictive value of IL-18 depends on hyperglycemia.[62]

Interleukin-18 and cardiovascular disease

Studies[53,63] regarding associations between IL-18 and stable atherosclerosis have yielded conflicting results. One study showed that elevated levels of IL-18 were associated with the presence of subclinical atherosclerosis (evaluated with intima media thickness of the carotid artery), also after adjustment for traditional risk factors, CRP and IL-6.

On the other hand, in three large studies[48,64,65] elevated levels of IL-18 were associated with carotid intima media thickness in univariate analyses, but not after adjustment for traditional risk factors.

Also data regarding IL-18 as a potential predictor of future cardiovascular events have so far been conflicting. In patients with known coronary artery disease, circulating IL-18 levels as well as polymorphisms in the IL-18 gene were associated with future cardiovascular mortality.[53]

However, another large population based study[66] with a follow up of 11 years showed that increased levels of IL-6 and CRP, but not IL-18 were associated with future coronary events. Furthermore, a recent study from five European prospective CVD cohorts showed no association between polymorphisms in the IL-18 receptor genes and cardiovascular risk.

To date, only three studies[62,67,68] have prospectively evaluated IL-18 as a potential predictor of cardiovascular events in populations with the metabolic syndrome .

In a large cohort[67] consisting of men and women with known coronary artery disease, IL-18 was the only independent predictor of cardiovascular mortality in a subgroup with the metabolic syndrome, even after adjustment for CRP, IL-6 and fibrinogen.

In line with these results, Troseid et al[68] showed that IL-18 was a strong and independent predictor of cardiovascular events in elderly men with the metabolic syndrome, even after adjustment for CRP and IL-6, and with a synergistic effect of IL-18 and fasting glucose in the cardiovascular risk prediction.

Potential mechanisms for interleukin-18 in the metabolic syndrome and atherosclerosis

Interleukin-18 in atherosclerotic lesions

IL-18 has been shown to be highly expressed in atherosclerotic plaques, mainly in plaque macrophages, and in particular, in unstable plaques. IL-18 is thought to exert its main pro-atherogenic effects by inducing IFN-γ production, which potentiates the inflammatory process and may lead to thinning or inhibition of the fibrous cap formation, resulting in vulnerable, rupture-prone plaques. Furthermore, IL-18 seems to increase the expression of matrix metalloproteinases in vascular cells and macrophages, which might also contribute to plaque destabilisation.[53]

Results from a recent study[69] using a rat model with metabolic syndrome showed, IL-18 overexpression aggravated insulin resistance, increased vascular

inflammation and promoted remodeling by enhanced infiltration of macrophages and increased medial thickness in the aortic wall.

Therefore, IL-18 leads to plaque destabilization and has also been shown to cause cardiac dysfunction.

Interleukin-18 in adipose tissue

The classical perception of adipose tissue as a passive storage place of fatty acids has gradually been replaced by the notion of adipose tissue, and visceral fat in particular as an active endocrine organ and a potential cause of the metabolic syndrome, in part mediated by release of a large number of metabolically active substances known as adipokines which are involved in inflammation, thrombosis, insulin sensitivity and energy balance.[53]

Human preadipocytes and adipocytes of all stages have been shown to spontaneously express and secrete IL-18. Of note, in obese individuals there is an increased expression of IL-18 in adipose tissue, and a 3-fold increased secretion from adipocytes compared with lean controls. Interestingly, experimental hyperglycemia has been shown to increase the expression of IL-18 in adipocytes, an effect which was even more pronounced in the presence of intermittent hyperglycemia. IL-18 in combination with a hyperglycemic proinflammatory milieu has been shown to trigger Th1 activation and IFN-γ production, both in adipose tissue and in the atherosclerotic plaque which explains the strong association of IL-18 with metabolic syndrome.[53]

Interleukin-18 as a potential therapeutic target

Effects of life style interventions

Lifestyle interventions consisting of diet and exercise have been shown to improve several cardiovascular risk factors including the metabolic syndrome and to reduce the risk of developing type 2 diabetes. Hence, current guidelines for management of the metabolic syndrome highlight the combination of increased physical activity (at least 30 minutes on most days of the week) and improved diet (decreased intake of saturated fat and simple carbohydrates, increased intake of fruits, vegetables, whole grain and fish) to achieve a sustained weight loss and reversal of the components of the syndrome.[53]

Weight loss mediated by calorie-restricted diet intervention was reported to decrease IL-18 levels in obese women. Furthermore, combined interventions with diet and exercise have been shown to reduce IL-18 levels in both obese men and women. Aerobic exercise has been reported to reduce levels of CRP and IL-18 in subjects with type 2 diabetes. Furthermore, exercise performed on rowing ergometer reduced adipose tissue expression of IL-18 in obese subjects.[53]

Although life style interventions such as diet and exercise have been shown to reduce levels of IL-18 in populations with and without the metabolic syndrome, it remains to demonstrate that such a reduction translates into reduced incidence of diabetes and cardiovascular events.

Effects of drug therapy

Several drugs are relevant in the management of the metabolic syndrome, including the most commonly used first line drugs recommended in current guidelines, that is statins and Angiotensin Converting Enzyme (ACE)-inhibitors /Angiotensin II (ATII) receptor antagonists.

The effects of statin therapy on IL-18 levels have been conflicting. Some studies[70,71] have shown reduced circulating levels of IL-18 in statin treated patients with hypercholesterolemia. On the other hand, one study[72] showed no effect of 20 months treatment with atorvastatin in patients with stable coronary artery disease. Moreover, statin therapy has consistently been reported to increase IL-18 in peripheral mononuclear cells. Hence, the effect of statins on IL-18 levels remains elusive.[53]

Although ACE-inhibitors and ATII receptor antagonists have been reported to have several anti-inflammatory properties, very few studies have evaluated the effect of these compounds on IL-18 levels.

Since IL-18 is subject to several regulatory steps including cleavage by caspase-1, inactivation by IL-18 binding protein, and signaling via the β chain of the IL-18 receptor, it will be crucial to clarify to what extent circulating levels of total IL-18 relate to the biological actions of the cytokine. Finally, strategies for blocking IL-18 activity are currently investigated in various pathophysological conditions such as sepsis and heart failure, and could potentially represent future therapeutic tools for the metabolic syndrome and its consequences.[53]

IL-18 and inflammatory markers:

Several cross-sectional studies have shown that acute-phase reactants such as C-reactive protein (CRP) and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α associate with features of the metabolic syndrome such as body mass index (BMI)/waist circumference, measures of insulin resistance/plasma insulin concentration, hypertension, and dyslipidemia. However, it is uncertain whether the association of inflammatory markers with metabolic syndrome is independent of measures of obesity and insulin resistance when they are included in a risk prediction model.[48]

Inflammation and activated innate immunity are thought to play an important role in the development of atherosclerosis and diabetes and may represent a unifying link between metabolic syndrome, type 2 diabetes, and CVD.[48]

In conclusion, IL-18 is a recently described member of the IL-1 cytokine superfamily, and is now recognized as an important regulator of innate and acquired immune responses. It appears that IL-18 functions as a pleiotropic proinflammatory cytokine, playing an early role in the inflammatory cascade. It may form a link between metabolic syndrome and atherosclerosis because IL-18 is highly expressed in atherosclerotic plaques, and a role in plaque destabilization has been suggested.[48]

There is ample evidence, that IL-18 levels may be linked with metabolic risk factors, although the role of IL-18 in the metabolic syndrome has not been adequately explored. IL-18 levels have been associated with adiposity and insulin

resistance and are increased by acute hyperglycemia in humans through an oxidative mechanism. Patients with type 2 diabetes have higher IL-18 levels than matched non-diabetic subjects.[48]

IL-18 was demonstrated as an independent predictor of adverse events in metabolic syndrome for the first time in an Australian study in 2007. The association was independent of the major determinants of metabolic syndrome, namely obesity and insulin resistance. Further adjustment for hs-CRP and IL-6 levels did not attenuate the relationship between IL-18 and metabolic syndrome.[20]

As evidenced by the preceding review of literature, IL-18 and metabolic syndrome seem to have an estranged relationship with numerous studies displaying contrasting results. Even in the face of compelling evidence, its association is still hiding under a blanket of doubt and warrants further prospective studies.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with metabolic syndrome during the period of January 2010 to December 2010.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2010 to December 2010.

Method of collection of data

Source of Data

Patients admitted in the wards of Medicine Department or attending the Medicine OPD/executive health check-up schemes on Mondays, Wednesdays and Fridays at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied.

Sample size

Hundred (100) patients with metabolic syndrome were selected for the study.

Sampling procedure

The sample size was calculated based on the formula as mentioned below.

$n = 4 X p X q / d^2$

Where p = Prevalence (Prevalence of the disease which was taken as 50% as no records were available regarding the study).

q = 100 – p

d = Absolute error taken as 10%

$n = 4 X 50 X 50 / 10^2$

n = 100

Every third patient fulfilling the inclusion criteria will be included in the study.

Selection criteria

Inclusion Criteria

- Age above 18 years.
- Patients with metabolic syndrome based on IDF criteria specific for south Asians.

Exclusion Criteria

- Patients with chronic inflammatory conditions like rheumatoid arthritis, systemic lupus erythematosis and scleroderma.

IDF criteria for the diagnosis of metabolic syndrome

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

- Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups)

Plus any two of the following four factors:

- Raised TG level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If FBS is above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Country /Ethnic group		Waist circumference
Europids: In USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cms
	Female	≥ 80 cms
South Asians: Based on Chinese, Malay and Asian Indian population	Male	≥ 90 cms
	Female	≥ 80 cms
Chinese	Male	≥ 90 cms
	Female	≥ 80 cms
Japanese	Male	≥ 90 cms
	Female	≥ 80 cms
Ethnic South and Central Americans	Use South Asian recommendation until more specific data are available	
Sub Saharan Africans	Use European data until more data are available	
Eastern Mediterranean and middle east (Arab) populations	Use European data until more data are available	

Procedure

The study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Belgaum. Patients admitted in the wards of Medicine Department or attending the Medicine OPD/executive health check-up schemes on Mondays, Wednesdays and Fridays at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were evaluated based on selection criteria. The selected patients were briefed about the nature of the study and a written informed consent was obtained (Annexure–I).

Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma (Annexure-II). A thorough clinical examination was conducted and the findings were also recorded.

Body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index in the range of less than 18.5 kg/m^2 were considered as underweight, 18.5 to 24.9 kg/m^2 were considered as normal, 25.0 to 29.9 kg/m^2 were considered as overweight and more than 30 kg/m^2 were considered as obese.[73-75]

The waist circumference was measured using a standard measuring tape in Cms. Waist circumference of ≥ 90 cms in males and ≥ 80 cms in females was considered as abnormal.

Investigations such as fasting blood sample for estimation of IL-18, hsCRP, blood glucose, lipid profile (total cholesterol, triglycerides, HDL, LDL) and insulin levels were done. Others tests like electrocardiogram was done.

Estimation of IL-18 was done using standard recombinant IL-18 enzyme linked immuno sorbent assay (ELISA) kit. Interleukin-18 levels above 216 pg/mL were considered as abnormal.[76]

Fasting blood sample was drawn for measuring plasma insulin levels and insulin levels were measured by microparticle enzyme immune assay (MEIA) method. Insulin resistance was calculated by HOMA IR;

$$\frac{\text{Fasting Insulin (}\mu\text{U/L) X Fasting plasma glucose (mmol/L)}}{22.5}$$

Homa IR

Patients were considered as insulin resistant if HOMA IR was more than 3.8.[77,78]

Subjects also underwent other investigations like fasting lipid profile.

Statistical analysis

The results were tabulated and the data was analysed using rates, ratios and percentages of different clinical manifestations. The data was compared using chi-square test, 'Z' test and student 't' test. A 'p' value of less than 0.05 was considered as statistically significant.

Chapter 5

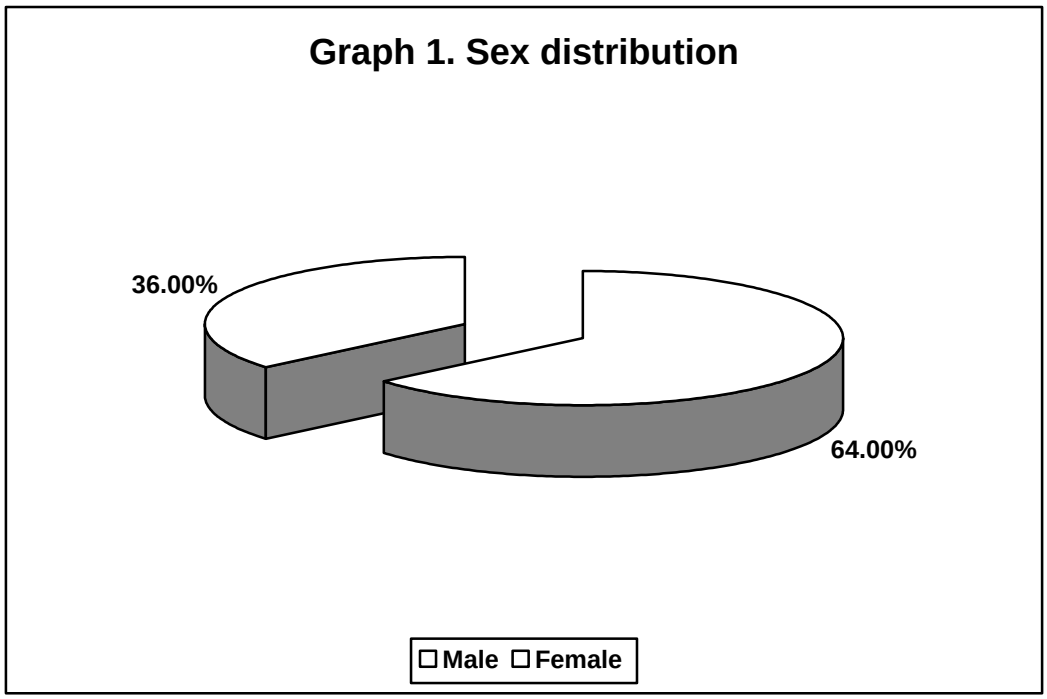
Results

RESULTS

The present study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients of metabolic syndrome. The data obtained was tabulated as below.

Table 1. Gender

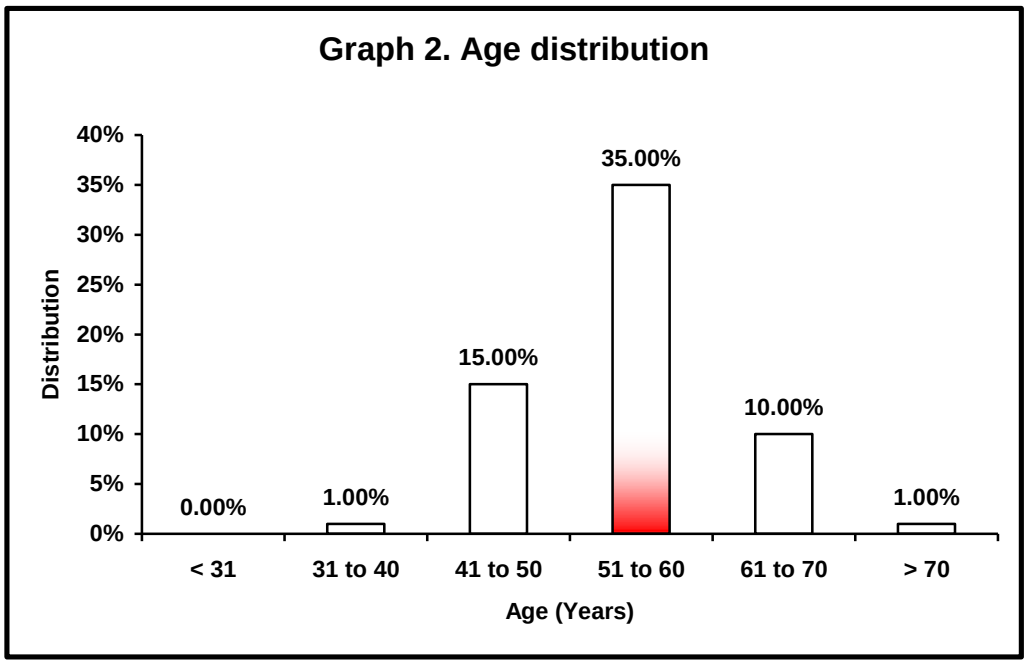
Gender	Distribution (n=100)	
	Number	**Percentage**
Male	64	64.00
Female	36	36.00
Total	**100**	**100.00**



In the present study, males accounted for 64 % (n=64), whereas females accounted for 36% (n=36).

Table 2. Age distribution

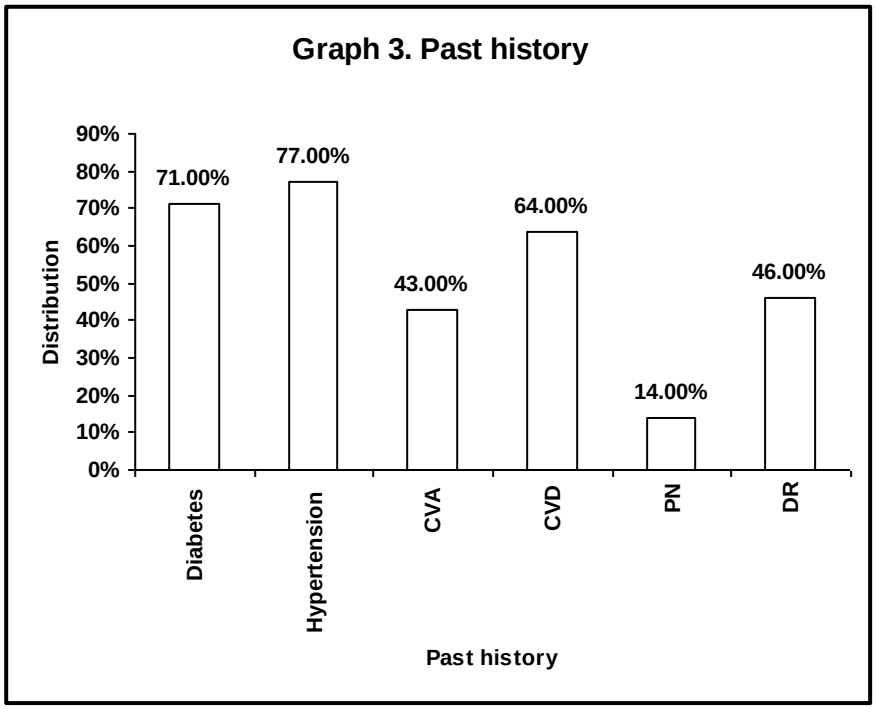
Age (Years)	Distribution (n=100)	
	Number	**Percentage**
< 31	0	0.00
31 to 40	1	1.00
41 to 50	15	15.00
51 to 60	35	35.00
61 to 70	10	10.00
> 70	1	1.00
Total	**62**	**62.00**



The above table, shows the distribution of subjects according to age. Majority of the subjects were between 51 and 60 years accounting for 35% (n=35), with 15 and 10 subjects between 41-50 and 61-70 respectively. Only a small number were below 40 or above 70 years (n=1, n=1 respectively). The mean age for the study population was 60.30 ± 9.43 years; among males, it was 60.20 ± 8.63 years and among females, it was 60.47 ± 10.84 years.

Table 3. Past history

Past history	Distribution (n=100)	
	Number	**Percentage**
Diabetes	71	71.00
Hypertension	77	77.00
Cerebrovascular accident	43	43.00
Cardiovascular disease	64	64.00
Diabetic peripheral neuropathy	14	14.00
Diabetic retinopathy	46	46.00



The study population was screened for the presence of diabetes, hypertension, cerebrovascular accidents and coronary artery disease. Diabetics were further examined for diabetic retinopathy and peripheral neuropathy. Diabetes accounted for 71 subjects (71%); whereas 77% (n=77) were hypertensive. Forty three patients reported a history of cerebrovascular accident and 64 had a significant past history suggestive of coronary artery disease. Of the 71 diabetic patients, 46 of them were found to have diabetic retinopathy and 14 were found to have diabetic peripheral neuropathy**.**

Table 4. Body mass index

Body mass index (Kg/m^2)	Distribution (n=100)	
	Number	**Percentage**
< 18.5	0	0.00
18.5 - 24.99	1	1.00
25 - 29.99	53	53.00
> 30	46	46.00

In the present study, 53 subjects were in the pre-obese group with a BMI between 25 to 29.99 kg/m^2 and 46 patients were obese with a BMI of > 30 kg/m^2. Only one patient had a normal BMI between 18.5-24.99 kg/m^2. The mean BMI of the study population was 29.69 ± 2.45 Kg/m^2.

Table 5. Waist circumference

Waist circumference	Distribution (n=100)	
	Number	**Percentage**
Normal	0	0.00
Abnormal	100	100.00
Total	**100**	**100.00**

In accordance with the IDF criteria for South Asians, waist circumference of ≥ 90 cms in males and > 80 cms in females was regarded as abnormal. All the subjects in the study had an abnormal waist circumference. The mean waist

circumference for the study population was found to be 102.06 ± 5.75 cms. Males had a mean waist circumference of 102.38 ± 4.58 cms and females had a mean waist circumference of 101.50 ± 7.44 cms.

Table 6. Blood pressure

Blood pressure	Mean BP (mm Hg)	
	Mean	**SD**
Systolic	142.36	15.57
Diastolic	90.06	9.60

The mean blood pressure in this study was 142.36 ± 15.57 mm Hg systolic and 90.06 ± 9.60 mm Hg diastolic.

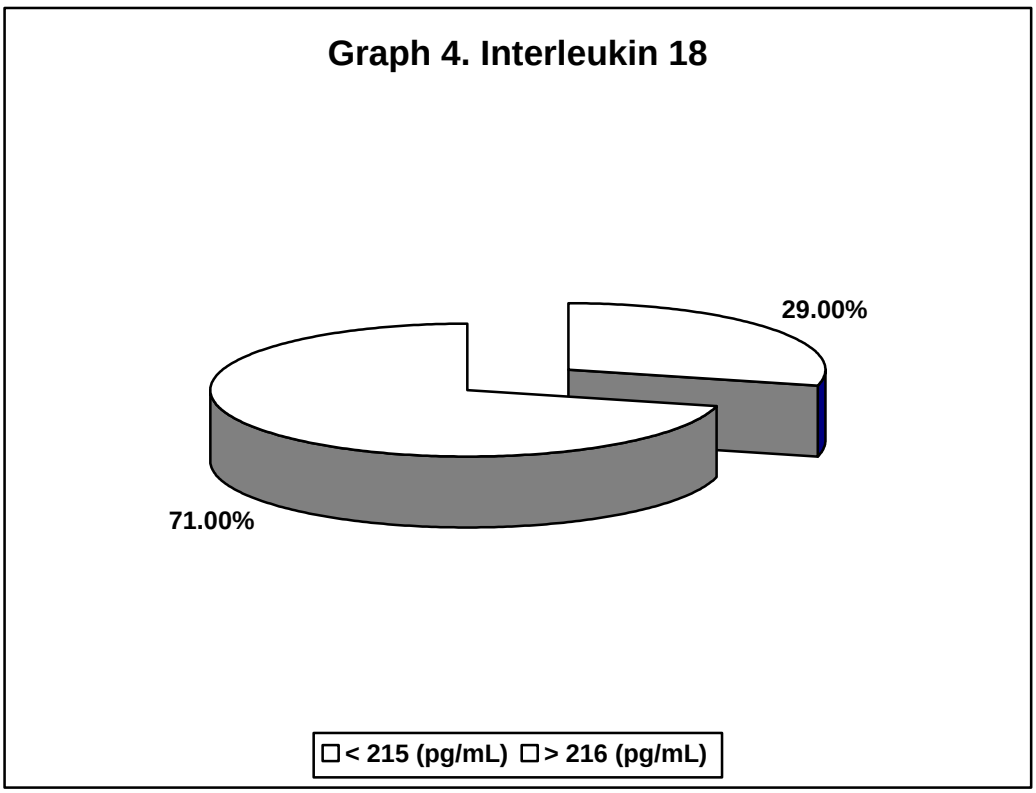
Table 7. Fasting blood sugar

FBS Levels (mg/dL)	Distribution (n=100)	
	No.	**Percentage**
< 100	3	3.00
> 100	97	97.00
Total	**100**	**100.00**

In accordance to the IDF criteria for diagnosis of metabolic syndrome, a Fasting blood sugar of > 100 mg/dL was considered abnormal. In the study, 97 subjects had an abnormal fasting blood sugar with a mean fasting blood sugar level of 142 ± 28.8 mg/dL.

Table 8. Interleukin 18

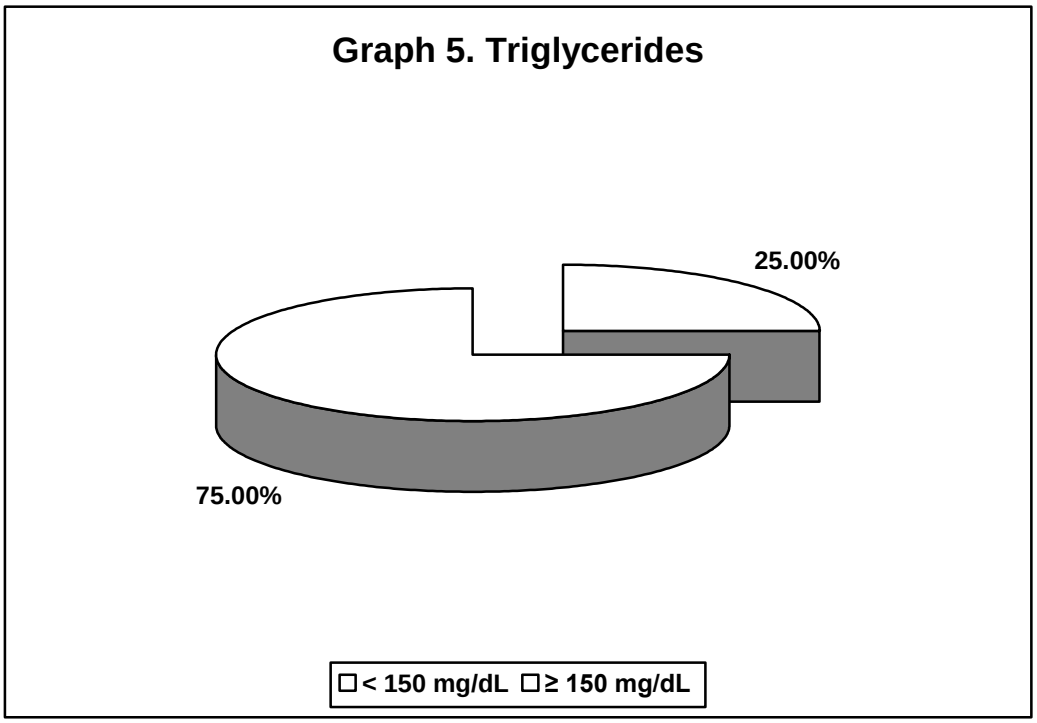
IL-18 (pg/mL)	Distribution (n=100)	
	Number	**Percentage**
< 215	29	29.00
≥ 216	71	71.00
Total	**100**	**100.00**



Using the standard MBL recombinant human IL-18 ELISA kit, values of ≥ 216 pg/mL was considered abnormal. In the present study, 71 patients (71%) were found to have an elevated IL-18 level whereas 29 subjects had an IL 18 ≤ 215 pg/mL.

Table 9. Triglycerides

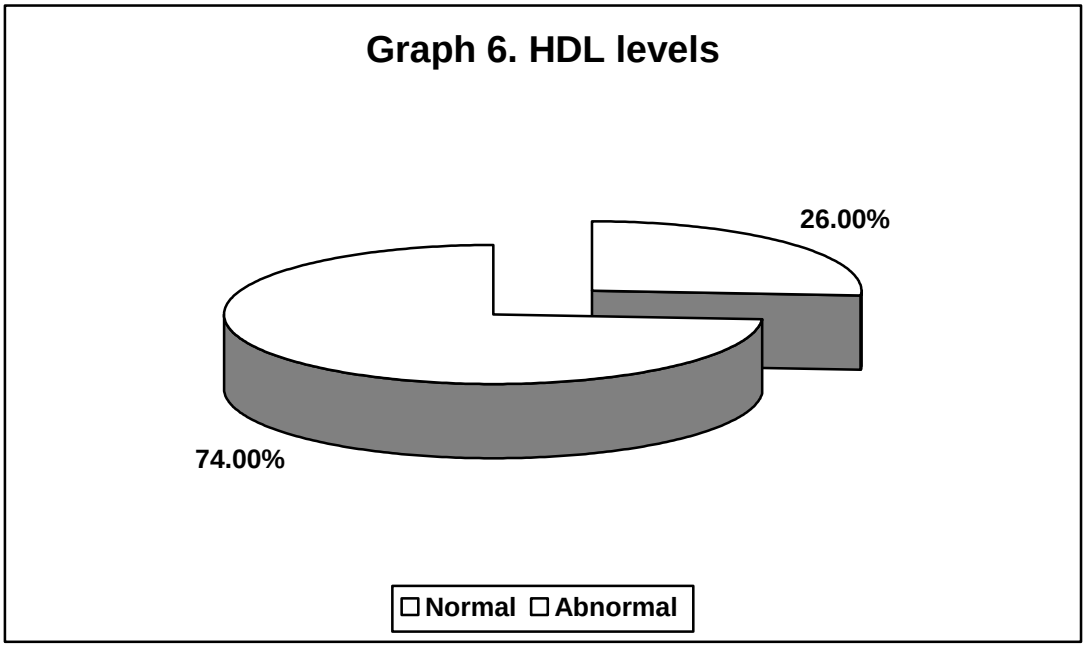
Triglyceride levels (mg/dL)	Distribution (n=100)	
	Number	Percentage
< 150	25	25.00
≥ 150	75	75.00
Total	**100**	**100.00**



In keeping with IDF criteria for diagnosis of metabolic syndrome, A Triglyceride level of ≥150mg/dL was considered as abnormal. In the present study, 75 subjects (75%) were found to have an abnormal TG as opposed to the remaining 25 subjects who had a Triglyceride level of < 150 mg/dL. The mean Triglyceride levels in this study was 166.16 ± 40.41 mg/dL.

Table 10. High density lipoprotein

HDL Levels (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal	26	26.00
Abnormal	74	74.00
Total	**100**	**100.00**



IDF criteria for the diagnosis of metabolic syndrome considers an HDL level of < 50 mg/dL in females and < 40mg/dL in males as abnormal. In the present study 74 subjects were found to have abnormal HDL levels whereas 26 subjects were found to be normal. The mean HDL levels of this study was 41.49 ± 9.74 mg/dL.

Table 11. HOMA-IR

HOMA-IR Levels	Patients	
	Number	**Percentage**
< 3.80	0	0.00
> 3.80	100	100
Total	**100**	**100**

HOMA-IR was considered to be abnormal at levels in excess of 3.80. In the present study, all the patients had an elevated HOMA-IR indicating insulin resistance. The mean HOMA-IR levels in this study was 15.53 ± 7.94.

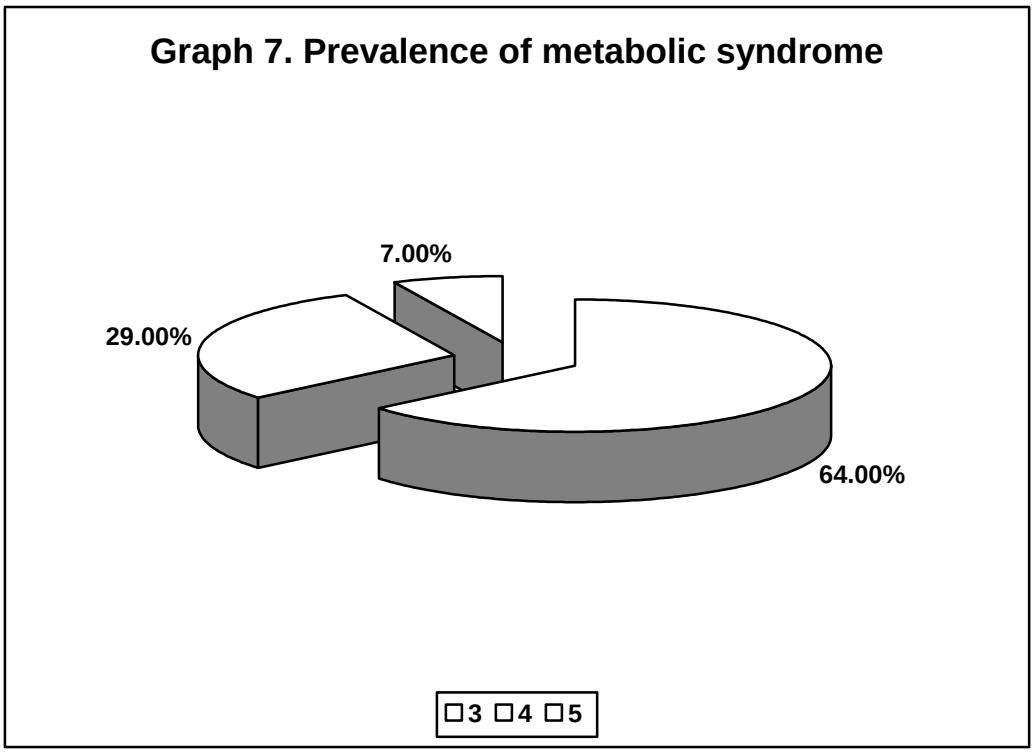
Table 12. HsCRP

hs-CRP (mg/dL)	Distribution (n=100)	
	No.	**Percentage**
< 3	0	0.00
> 3	100	100.00
Total	**100**	**100.00**

hs-CRP has been well established as a prognostic marker of adverse cardiovascular events and a value in excess of 3 mg/L was considered as abnormal. In the present study, all the subjects had an abnormal hs-CRP with a mean of 19.96 ± 9.59 mg/L.

Table 13. Prevalence of metabolic syndrome

Number of Metabolic syndrome components	Distribution (n=100)	
	Number	**Percentage**
3	64	64.00
4	29	29.00
5	7	7.00
Total	100	100.00



As regards the prevalence of components of the metabolic syndrome, 64 subjects (64%) had three components of the metabolic syndrome, 29 subjects had four components of the metabolic syndrome and 7 subjects had all five components of the metabolic syndrome.

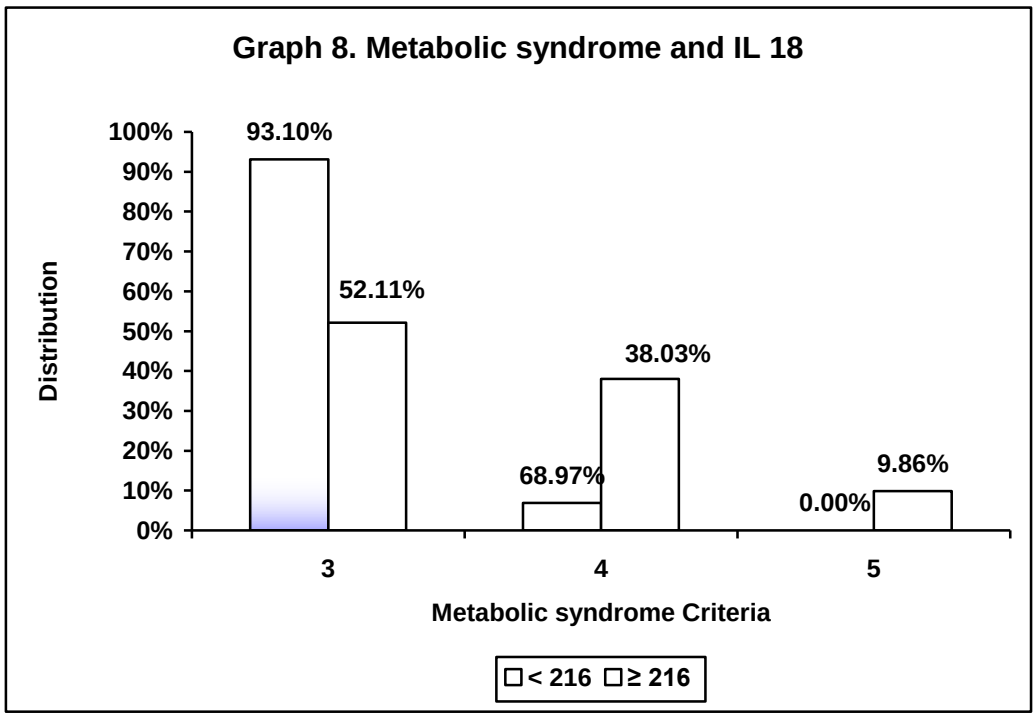
Table 14. Correlation between IL – 18 and components of metabolic syndrome

Parameters	Interleukin – 18 (pg/mL) ≤ 215 (n = 29) No	%	≥ 216 (n = 71) No	%	x_1^2	p
TG (mg/dL)						
< 150	13	44.83	12	16.90	8.564	0.003
> 150	16	55.17	59	83.10		
Total	**29**	**100.00**	**71**	**100.00**		
HDL(mg/dL)						
< 40 or < 50	15	51.70	51	71.80		
> 40 or > 50	14	48.30	20	78.20	3.710	0.054
Total	**29**	**100.00**	**71**	**100.00**		
DM						
Absent	11	37.93	18	25.35		
Present	18	62.07	53	74.65	1.582	0.208
Total	**29**	**100.00**	**71**	**100.00**		
Hypertension						
Present	19	65.52	58	81.69		
Absent	10	34.48	13	18.31	3.041	0.081
Total	**29**	**100.00**	**71**	**100.00**		
FBS						
< 100	2	6.90	1	1.41		
> 100	27	93.10	70	98.59		0.662
Total	**29**	**100.00**	**71**	**100.00**		

IL-18 was correlated with each of the components of the metabolic syndrome. Significant correlation was observed between IL-18 and TG levels with 59 (83%) subjects having raised IL-18 as well as TG levels. Strong correlations were observed between HDL levels and IL-18 with 51 subjects (71.8%) of patients who had an abnormal HDL and IL-18. A significant 58 (81.69%) hypertensives had an abnormal IL-18 ($p=0.081$) whereas 53 diabetics had an abnormal IL-18 which was not statistically significant. Of the 97 subjects with an abnormal FBS, 71 had a raised IL-18 level, but this was also not statistically significant.

Table 15. Metabolic syndrome and IL-18

Number of Metabolic syndrome components	Interleukin-18(pg/mL)			
	≤ 216 (n=29)		≥ 216 (n=71)	
	Number	Percentage	Number	Percentage
3	27	93.10	37	52.11
4	2	6.90	27	38.03
5	0	0.00	7	9.86
Total	**29**	**100.00**	**71**	**100.00**
x^2= 15.146		DF=2		p=0.001

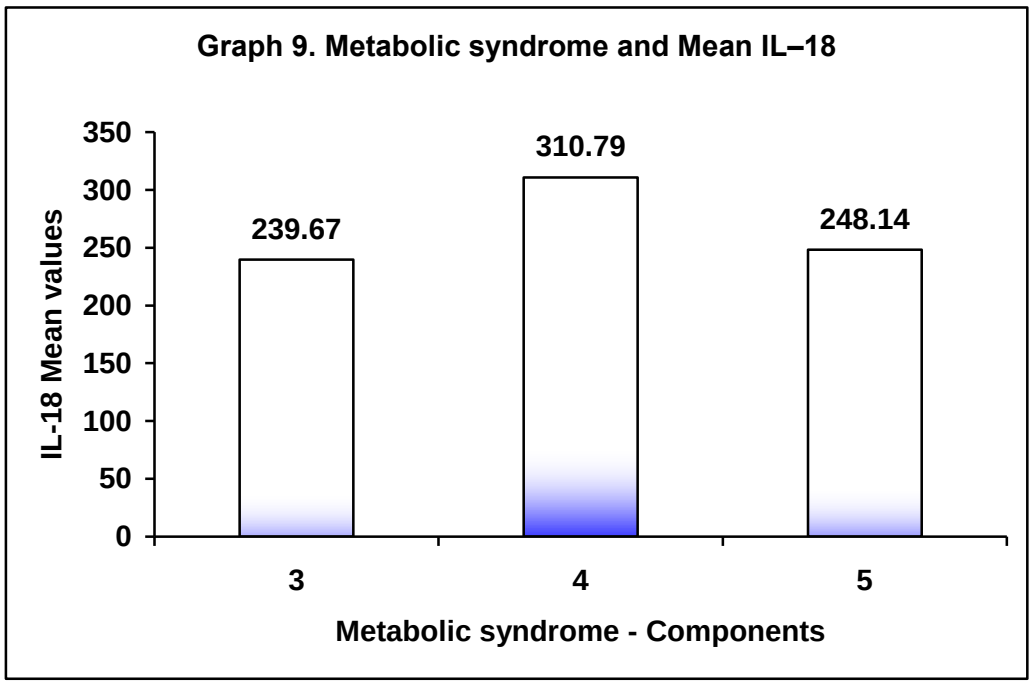


On comparing the number of metabolic syndrome components with IL-18, a statistically significant association was observed with 37 subjects (57.8%) with 3 components of the metabolic syndrome also having an abnormal IL-18 levels. A staggering 27 patients (93.1%) with 4 components had a raised IL-18, whereas all the patients with 5 components of metabolic syndrome had raised IL-18 levels. (p=0.001)

Table 16. Metabolic syndrome and Mean IL – 18

Number of Metabolic syndrome components	IL-18 (pg/mL)	
	Mean	**SD**
3	239.67	59.94
4	310.79	72.53
5	248.14	32.65

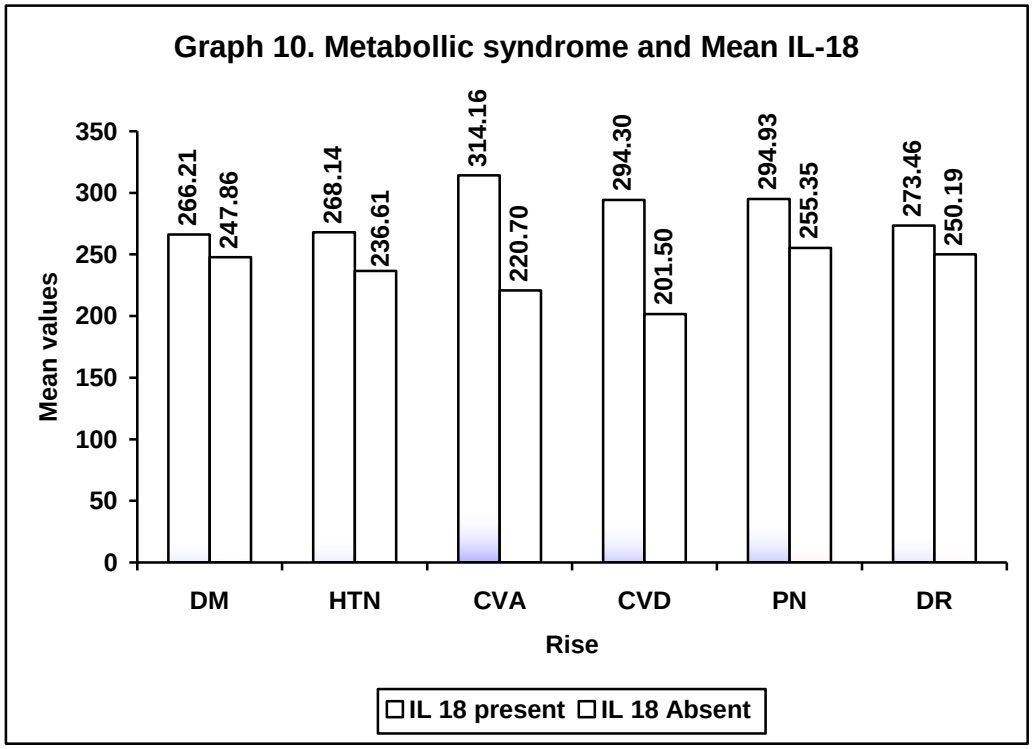
ANOVA F_{39}=13.038 p<0.001



The mean levels of IL-18 were significantly higher in patients with 4 components of metabolic syndrome as compared with those with 3 components of metabolic syndrome (310.79 ± 72.53 pg/mL vs 239.67 ± 59.94 pg/mL). The mean IL-18 levels in the patients with five components was also higher than those with 3 components of the metabolic syndrome (248.14 ± 32.65 vs 239.67 ± 59.94) (p<0.001).

Table 17. Metabolic syndrome and Mean IL-18

Complications of Metabolic syndrome	Present		Absent		't' value	DF	'p' value
	Mean	SD	Mean	SD			
DM	266.21	73.51	247.86	58.87	1.196	98	0.235
HTN	268.14	70.25	236.61	63.80	1.927	98	0.057
CVA	314.16	62.15	220.7	43.49	8.846	98	**<0.001**
CVD	294.3	61.75	201.5	35.31	8.277	98	**<0.001**
PN	294.93	88.34	255.35	35.25	1.997	98	**0.049**
DR	273.46	81.03	250.19	57.19	1.677	98	0.097



In the comparison of IL-18 with complications of metabolic syndrome, mean IL-18 levels were found to be higher in all patients with complications as opposed to patients without. Though, statistically significant correlation was observed in patients with Cerebrovascular accidents and with cardiovascular disease. ($p<0.001$)

Table 18. Correlation IL–18 and metabolic syndrome

Components		Interleukin-18 (pg/mL)		't' value	DF	'p' value
		Mean	SD			
BMI	At risk	-	-			
	Overweight	237.15	56.01	4.095	98	**<0.001**
	Obese	289.55	74.08			
WC	Normal	-	-			
	Abnormal	260.89	69.79			
TG	Normal	218.96	50.00	3.682	98	**<0.001**
	Abnormal	274.87	70.10			
HDL	Normal	228.65	51.20	3.499	98	**<0.001**
	Abnormal	277.50	72.52			

The mean IL-18 levels in patients who were overweight was 237.15 ± 56.01 pg/mL whereas in obese patients, the mean IL-18 was 289.55 ± 74.08 pg/mL ($p<0.001$). Both TG (274.87±70.1 pg/mL vs 218.96±50 pg/mL) and HDL (277.5± 72.52 mg/dL vs 228.65±51.20 mg/dL) showed significantly higher IL-18 levels in patients who had abnormal levels as per the IDF criteria specific for south Asians ($p<0.001$).

Table 19. Correlation IL–18 and metabolic syndrome

Metabolic syndrome		IL-18 < 216		IL-18 > 216		't' value	DF	'p' value
		Mean	SD	Mean	SD			
BP (mm Hg)	SBP	136.90	15.82	144.59	15.01	2.607	98	**0.011**
	DBP	86.76	10.02	91.41	9.15	2.487	98	**0.015**
FBS (mg/dL)		128.62	21.76	147.46	29.65	2.907	98	**0.005**
HOMA-IR		10.36	9.78	17.65	5.93	4.743	98	**<0.001**
Insulin (μU/L)		20.56	5.25	37.87	7.25	3.278	98	**0.001**
WC (cms)		98.86	5.32	103.37	5.43	3.839	98	**<0.001**

Among the patients with abnormal levels of IL-18, significantly higher levels of HOMA-IR (17.65 ± 5.93 vs 10.36 ± 9.78) and waist circumference (103.37cms vs 98.86 cms) was observed which was statistically significant ($p<0.001$). The mean systolic (144.59 ± 15.01 mm Hg vs 136.9 ± 15.82 mm Hg) and mean diastolic blood pressures(91.41 ± 9.15 mm Hg vs 86.76 ± 10.02 mm Hg) were higher in patients with an abnormal IL-18 level. ($p= 0.011, 0.015$ respectively). A gross difference was observed in the mean fasting blood sugars (147.46 ± 29.65 mg/dL vs 128.62 ± 21.76 mg/dL) and fasting insulin levels (37.87 ± 7.25 μU/L vs 20.56 ± 5.25 μU/L) between the patients with IL 18 ≥ 216 pg/mL as opposed to patients with IL-18 < 216 pg/mL ($p=0.005, 0.001$).

Table 20 . Correlation co-efficient between IL-18 and risk factors

Risk factors	Distribution (n=100)	
	γ	'p' value
Systolic blood pressure	0.364	**<0.001**
Diastolic blood pressure	0.307	**0.002**
Fasting blood sugar	0.421	**<0.001**
HOMA-IR	0.646	**<0.001**
Insulin level	0.403	**<0.001**
Waist circumference	0.490	**<0.001**
Body mass index	0.457	**<0.001**
Age	0.268	**0.007**

The strongest correlation of IL-18 was observed with HOMA-IR with a correlation coefficient of 0.646 ($p \leq 0.001$) which reaffirms the role of inflammation in the pathogenesis of insulin resistance. Correlation coefficients of 0.490 and 0.457 were observed with waist circumference and BMI respectively which were also statistically significant. Fasting blood sugar levels ($\gamma=0.421$), insulin levels ($\gamma=0.403$), systolic blood sugar levels ($\gamma=0.364$), diastolic blood pressure ($\gamma=0.307$) showed definite, albeit weaker, associations with IL-18 which were all statistically significant ($p \leq 0.001$).

Chapter 6

Discussion

DISCUSSION

Metabolic syndrome is the fore-runner of dire consequences both in terms of morbidity and mortality. It has been established beyond doubt that, metabolic syndrome spawns numerous complications like coronary artery disease,[12,79-81] Type II Diabetes mellitus,[79,80] Non-alcoholic fatty liver,[82] Polycystic ovarian disease.[83]

The diagnosis of metabolic syndrome has to its discredit a great deal of heterogeneity and ambiguity, thereby rendering this syndrome immune to accurate estimations of prevalence and complications. In the absence of a diagnostic test, various systems of definitions have been proposed each with its unique cut-off points and individual factors. These include the WHO, EGIR, NCEP-ATP III and IDF criteria, each with its advantages and disadvantages. In this miasma of doubt, accurate predictions of complications in this subset of patients, becomes a task bordering the impossible.

Recent developments in the pathogenesis of metabolic syndrome have focused on an immunologic component, with its accompanying cytokines and other inflammatory markers, to play a crucial role in the evolution and development of complications. Highly sensitive CRP (hsCRP) and Interleukin – 6 (IL-6) have been established as markers of atherosclerosis and predictors of adverse cardiovascular events in these patients.[84-86] Interleukin-18 has only recently been explored as a potential marker of diagnostic as well as prognostic importance in metabolic syndrome, because of an apparent advantage over conventional markers in the setting of hyperglycemia.[20]

The present study was done on 100 subjects of metabolic syndrome which was diagnosed using the IDF criteria, 2005. Of the total study population, males outnumbered the females (64% versus 36%). In a study done in Perth, Australia, using four groups of subjects according to the presence of the individual components of the metabolic syndrome, 60.7% were males in the cohort of subjects with metabolic syndrome as diagnosed by the NCEP-ATP III criteria.[20]

Majority of the subjects were between 51 and 60 years accounting for 35% (n=35), with 15 and 10 subjects between 41-50 and 61-70 respectively. Only a small minority were below 40 or above 70 years (n=1, n=1 respectively). The mean age for the study population was 60.30 ± 9.43; among males it was 60.20 ± 8.63 years and among females, it was 60.47 ± 10.84 years. In a study done in Australia, in 2005, the mean age for the cohort of patients with metabolic syndrome was 57.1 (55.3–58.9)[20]

Height and weight of subjects was measured and BMI was calculated. In the present study, 53 subjects were in the pre-obese group with a BMI between 25-29.99 kg/m^2 and 46 patients were obese with a BMI of > 30 kg/m^2. Only one patient had a BMI between 18.5-24.99 kg/m^2. The mean BMI of the study population was 29.69 ± 2.45 kg/m^2. In a study done in Norway, IL 18 was correlated with cardiovascular events in metabolic syndrome patients, the mean BMI in patients with metabolic syndrome was found to be 28.4 kg/m^2 (26.6-30.6).[62] In the National health statistics report of 2009, 29.8% of subjects were overweight and 65% of subjects were obese.[87] In a study of urban Indian population, they found 79.01% of subjects with a BMI of > 24.99kg/m^2.[88]

The relevant historical profile included a past history of Type II Diabetes mellitus, Hypertension, Cerebrovascular accidents or history suggestive of coronary heart disease. Diabetic patients were additionally examined for complications such as retinopathy and neuropathy. Diabetes accounted for 71 subjects (71%); whereas 77% (n=77) were hypertensive. 43 (43%) patients reported a history of cerebrovascular accident, 64(64%) had a significant past history suggestive of coronary artery disease. Of the 71 diabetic patients, 46 of them were found to have diabetic retinopathy and 14 were found to have diabetic peripheral neuropathy. In a similar study done in the University of Oslo, among patients with metabolic syndrome, 29% had diabetes, 40% had hypertension and 28% had previous cardiovascular disease (composite of coronary heart disease, cerebrovascular disease and peripheral vascular disease).[62] On the other hand, in a prevalence study of metabolic syndrome and its components in urban India, Diabetes was found in 82.01% of subjects and hypertension was found in 70.9% of patients.[89] In the CURES-34 study done in Chennai, India, 39.7 % of the subjects diagnosed with metabolic syndrome by the IDF criteria had Coronary artery disease. [90] In a study done on urban Indian population, Hypertension formed 70% of the subjects with metabolic syndrome. [91] This high prevalence of Diabetes and Hypertension, is supported by the fact that Diabetes and Hypertension have been found to be more widely prevalent in South Asians, thus, conferring a large and very real risk of adverse cardiovascular events and other attending complications.[89] The possible explanations for this inordinately high prevalence can be attributed to a high prevalence of obesity, insulin resistance

and a body fat structure that favours the development of metabolic syndrome, Diabetes and Hypertension.[92,93]

In 2005, IDF rolled out a new criteria for the diagnosis of metabolic syndrome which was aimed at being more widely applicable and easily reproducible. This criteria focused on waist circumference as a major determinant of metabolic syndrome and laid down region specific cut-off values. In accordance with the IDF criteria for South Asians, waist circumference of ≥ 90 cms in males and ≥ 80 cms in females was regarded as abnormal. All the subjects in the study had an abnormal waist circumference. The mean waist circumference for the study population was found to be 102.06 ± 5.75 cms. males had a mean waist circumference of 102.38 ± 4.58 cms and females had a mean waist circumference of 101.50 ± 7.44 cms. In the study done in University of Western Australia, mean waist circumference among subjects with metabolic syndrome was 96.4 (94.8–97.9); whereas a Norwegian study in 2009, had a study population with a mean waist circumference of 104 (99 - 109). Both these studies were done in europoid population which considered different cut-off values for waist circumference as given by IDF criteria, 2005.[20,62] In a study done on male population of south India, the mean waist circumference for subjects with metabolic syndrome according to the IDF criteria, was found to be 97.9 ± 6.40 cms.[94]

The mean blood pressure in this study was 142.36 mm Hg systolic and 90.06 mm Hg diastolic which is comparable to other studies[88] done on metabolic syndrome population in India.

Fasting blood sugar cut-offs have seen a steady decrement over the years. In accordance to the latest IDF criteria for diagnosis of metabolic syndrome, a Fasting blood sugar of > 100 mg/dL was considered abnormal. In the study, 97 subjects had an abnormal fasting blood sugar. The mean fasting blood sugar of the study population was found to be 142 ± 28.8 mg/dL. In an Australian study, exploring the association of interleukin 18 independent of obesity, mean fasting blood glucose was found to be 111.7 mg/dL (109-123mg/dL).[20] In yet another Scandinavian study, mean fasting blood glucose was also found to be 111.8 mg/dL (99.8 – 126.1mg/dL)[62] In a prevalence study of metabolic syndrome in urban India, mean fasting blood glucose was found to be 118.8 ± 42.31mg/dL.[94] Fasting blood glucose represents, albeit indirectly, the severity of insulin resistance and the glycemic control of the patient, both of which have been shown to predispose to the development of metabolic syndrome.[20,32] The reason for the higher mean fasting blood glucose level in this study can be explained by the fact that, 71% of the patients were known diabetics on medication, which may have been poorly controlled. The studies quoted above have mainly taken subjects with impaired fasting glucose with a relatively small percentage of known diabetics.

IL-18 was obtained using the standard MBL recombinant human IL-18 ELISA kit with values of >215 pg/mL considered as abnormal. In the present study, 71 patients were found to have an elevated Il-18 level (71%) whereas 29 subjects had a IL-18 ≤ 215 pg/mL. The mean IL-18 levels were found to be 260.89 ± 69.79 pg/mL. In various studies of IL-18 with metabolic syndrome, mean IL-18 have ranged from 292 pg/mL to 356 pg/mL.[20,62]

In keeping with IDF criteria for diagnosis of metabolic syndrome, A Triglyceride level of ≥ 150 mg/dL was considered as abnormal. In the present study, 75 subjects (75%) were found to have an abnormal TG as opposed to the remaining 25 subjects who had a Triglyceride level of < 150 mg/dL. Also, IDF criteria for the diagnosis of metabolic syndrome considers an HDL level of < 50 mg/dL in males and < 40mg/dL in females as abnormal. In the present study 74 subjects were found to have abnormal HDL levels whereas 26 subjects were found to be normal. The significant majority of the study population had abnormal lipids indicating a high prevalence of dyslipidemia and highlighting its contribution in the development of metabolic syndrome. The mean Triglyceride and HDL levels in this study was 166.16 ± 40.41 mg/dL and 41.49 ± 9.74 mg/dL respectively. In a survey done by the US Department of Health and Human services, Triglyceride levels and HDL levels were found to be abnormal in 31.4% and 24.7% respectively.[87] In another study done in New Delhi, India, the age-adjusted HDL levels were found to be low in 64.91% of subjects.[88] In a study done on Asian-indians (Chennai), abnormal TG and HDL levels were seen in 76% and >90% of the study population. Asian Indians were found not only to have low HDL, but also have a preponderance of small, dense, dysfunctional HDL particles that are associated with less efficient reverse cholesterol transport and less protection against CAD.[89] In a sub-study of the Chennai rural epidemiology study, abnormal Triglycerides and HDL was found in 25.2% and 63.5% of patients.[90] However, in a study done only on urban south Indian men, abnormal TG was seen in 45.2%, whereas abnormal HDL was seen in 70.3% of subjects.[94]

Insulin resistance is a central feature of metabolic syndrome. There are various measures of insulin resistance and HOMA-IR was used in this study. HOMA-IR was considered to be abnormal at levels in excess of 3.80. In the present study, all the patients had an elevated HOMA-IR indicating insulin resistance. The mean HOMA-IR was 15.53 ± 7.94. This is one of the few studies to consider HOMA-IR as the insulin sensitivity model and correlate it with IL-18.

hs-CRP has been well established as a prognostic marker of adverse cardiovascular events and a value in excess of 3 mg/L was considered as abnormal. In the present study, all the subjects had an abnormal hsCRP with a mean of 19.96 ± 9.59 mg/L. In a landmark study done at Harvard Medical school, Boston, mean CRP values of 3.38 mg/L was obtained in the patients with metabolic syndrome.[84] In a sub-study of the Framingham Offspring study, mean CRP values of 7.8 ±0.4 mg/L were observed.[84] In an Indian study, mean hsCRP levels were estimated in an urban Indian sample with metabolic syndrome and was estimated at 4.72 ± 0.71 mg/L.[91] The high levels of hs-CRP levels in this study indicates a study population at high risk of complications, which is reflected by the high prevalence of Diabetes and cardiovascular disease in these patients (71%, 64% respectively)

Correlation of BMI with Interleukin 18:

Obesity is the major determinant of metabolic syndrome and its consequences. Obesity not only fosters insulin resistance, but also engenders dyslipidemia which is another risk factor for metabolic syndrome. In this study BMI was significantly correlated with mean IL-18 levels; patients who were

over-weight (BMI 25 kg/m^2 - 29.99 kg/m^2) had a mean IL-18 of 237.15 ± 56.01 pg/mL whereas in obese patients (BMI ≥ 30 kg/m^2), the mean IL-18 was 289.55 ±74.08 pg/mL (p<0.001). In a landmark study investigating the role of IL-18 in metabolic syndrome, they found moderate correlation between IL-18 and BMI with a correlation coefficient of 0.26.[20] This can be explained by the fact that recent evidence indicates a central pathophysiologic role of visceral adiposity in metabolic syndrome, for which BMI is a poor measure.[92,93]

Correlation of IL-18 with components of the Metabolic syndrome:

All the patients in this study were found to have abnormal waist circumference levels as per IDF criteria specific for south Asians. In this study, significantly higher levels of waist circumference (103.37cms v/s 98.86 cms) was observed in patients with abnormal IL-18 levels with a correlation coefficient of 0.490, which was statistically significant (p<0.001). Other studies in this area, have found a correlation coefficient of 0.39 which is comparable with the present study.[20]

In patients with TG ≥ 150mg/dL (n=75), 59 (83.1%) of the patients had an abnormal IL-18 of ≥ 216 pg/mL. this was statistically significant (p=0.003). No significant correlations were seen with IL-18, among diabetics. Significant correlation was observed in patients with Hypertension, which accounted for 81.69% of subjects with an abnormal IL-18 (p=0.081). A vast majority (98.59%) of the patients with an abnormal Il-18 had a fasting blood glucose in excess of 100 mg/dL.

In the study conducted in Western Australia, the study populations was divided according to the presence of components of metabolic syndrome and then correlated with IL-18. Significant correlations were observed between IL-18 and all the components of metabolic syndrome with $p<0.001$.[20] In contrast, in the Prospective Epidemiological Study of Myocardial Infarction (PRIME) of apparently healthy European men aged 50 to 69 years, IL-18 levels did not associate with BMI and only weakly with HDL and triglycerides.[95]

In this study, the subjects with abnormal TG and HDL showed significantly higher IL-18 levels (274.87 ± 70.1 pg/mL v/s 218.96 ± 50 pg/mL, 277.5 ± 72.52 pg/mL v/s 228.65 ± 51.20 pg/mL respectively) ($p<0.001$). Among the patients with abnormal levels of IL-18, the mean systolic (144.59 ± 15.01 mm Hg v/s 136.9 ± 15.82) and mean diastolic (91.41 ± 9.15 mmHg v/s 86.76 ± 10.02 mmHg) blood pressures were higher in patients with an abnormal IL-18 level. ($p=0.011$, 0.015 respectively). A gross difference was observed in the mean fasting blood sugars (147.46± 29.65 v/s 128.62 ± 21.76 mg/dL), between the patients with IL-18 ≥ 216 pg/mL as opposed to patients with IL-18 < 216 pg/mL. ($p=0.005$, 0.001). These findings indicate a strong association of IL-18 with metabolic syndrome and mirrors the findings of other studies in this area.[20,62]

Correlation of IL 18 with insulin resistance

Insulin resistance has been regarded as the main culprit in the pathophysiology of metabolic syndrome. Among the patients with abnormal levels of IL-18, significantly higher levels of HOMA-IR (17.65 ± 5.93 v/s 10.36 ± 9.78) were observed which was statistically significant ($p<0.001$). A gross

difference was observed in the fasting insulin levels (37.87 ± 7.25 μU/L v/s 20.56 ± 5.25 μU/L) between the patients with IL-18 ≥ 216 pg/mL as opposed to patients with IL-18 <216 pg/mL (p=0.001). This study has shown the strongest association of HOMA-IR and IL-18 with a correlation coefficient of 0.646 which was statistically significant (p<0.001). Other studies in this area, have also shown that Insulin levels and waist circumference have high correlation coefficients (0.39, 0.2 respectively).[20] The higher correlation coefficient and mean HOMA-IR in this study, are a testimony to the widely prevalent Insulin resistance in Indian population and points to a definite association with IL-18.

Correlation of IL 18 with the complications of metabolic syndrome

Significant correlations were observed between mean IL-18 levels and the various components of metabolic syndrome. The mean IL-18 levels were found to be significantly higher in diabetics, hypertensives, patients with past H/o cerebrovascular accident, Coronary artery disease, diabetic retinopathy and diabetic peripheral neuropathy. These associations were statistically significant with hypertension (p=0.057), CVA (p≤0.001), CVD (p≤0.001) and diabetic peripheral neuropathy (p=0.049).

Interleukin -18 has been implicated in hypertension in various studies.[96] In the present study, the mean IL-18 levels were found to be significantly higher in hypertensives (268.14 ± 70.25 pg/mL v/s 236.61 ± 63.80 pg/mL) (p=0.057). In a sub study of Carotid Ultrasound Disease Assessment Study, IL-18 was significantly correlated with Blood pressure. (spearman rank coefficient of 0.18, p≤0.001).[20] A study done in Barcelona, Spain in 2006, showed significantly

higher values of IL-18 in hypertensive patients which was statistically significant (adjusted r^2=0.25, p=0.023).[97] This association has been explained by the fact that, experimental evidence indicates that the expression of IL-18 and/or its receptor can be induced by catecholamines or angiotensin, two factors that are involved in the pathophysiology of hypertension.[96]

In this study, the mean IL-18 levels were found to be significantly higher in diabetics (266.21 ± 73.51 pg/mL v/s 247.86 ± 58.87 pg/mL), though this was not found to be statistically significant. (p=0.235) In 2003, a study in Japan, observed significantly higher IL-18 concentrations in diabetics as compared to non-diabetics.[57] In the MONICA/KORA Augsburg Study, 1984–2002, elevated levels of IL-18 were associated with a significantly increased risk of type 2 diabetes after adjustment for age, sex, survey, BMI, systolic blood pressure, ratio of total cholesterol to HDL cholesterol, physical activity, alcohol intake, smoking status, and parental history of diabetes.[61]

In the present study, the mean IL-18 levels were found to be significantly higher in patients with past history of CVA (314.16 ± 73.51 pg/mL v/s 220.17 ± 43.49 pg/mL) which was statistically significant (p<0.001). In 2003, a polish study, investigated the association of IL 18 and acute ischaemic stroke and found higher serum IL-18 levels in stroke patients. This correlated with erythrocyte sedimentation rate (ESR), brain CT hypodense area volumes, and Scandinavian Stroke Scale and Barthel Index scores. They concluded that IL-18 is involved in stroke-induced inflammation and that initial serum IL-18 levels may be predictive of stroke outcome.[98]

In this study, the mean IL-18 levels were found to be significantly higher in patients with past history of CVA (294.3 ± 61.75 pg/mL v/s 201.5 ± 35.31 pg/mL) which was statistically significant ($p<0.001$). In 2002, a French study, showed Plasma IL-18 concentrations are increased in patients with acute coronary syndromes and correlate with the severity of myocardial dysfunction.[99] This was further proved by a study conducted in Japan in 2005 when they additionally showed that Plasma Interleukin-18 elevation preceded creatine kinase-MB elevation in myocardial infarction patients.[100] In a large prospective study in Germany, they showed that Serum IL-18 level is a strong independent predictor of death from cardiovascular causes in patients with coronary artery disease regardless of the clinical status at admission.[101] Most recently, a Norwegian study in 2009, proved a direct correlation between IL-18 and cardiovascular events, where, Cardiovascular events was a composite of fatal and nonfatal CVD, defined as myocardial infarction, revascularization procedures, aortic aneurism, peripheral arterial occlusive disease, and cerebrovascular events.[62] However, a large sub-study from the Dallas Heart study, showed that even though elevated IL-18 plasma levels correlated well with risk factors for atherosclerosis and with the metabolic syndrome, the association between IL-18 and atherosclerosis diminished after accounting for traditional cardiovascular risk factors which suggested that IL-18 does not add independently to detection of atherosclerotic burden in asymptomatic individuals.[48]

This study however, has shown a significant correlation between all the complications of metabolic syndrome except Diabetes ($p=0.235$). Fasting blood sugar levels ($\gamma=0.421$), insulin levels ($\gamma=0.403$), systolic blood pressure levels

(γ=0.364), diastolic blood pressure (γ=0.307) showed definite, albeit weaker, associations with IL-18 which were all statistically significant ($p \leq 0.001$). This indicates IL-18 to be a strong prognostic marker of metabolic syndrome with a reliable utility in the management of this heterogenous population.

Chapter 7

Conclusion

CONCLUSION

- Interleukin-18 levels were found to be significantly higher in patients with metabolic syndrome.

- There was a direct relationship between IL-18 levels and the number of components of metabolic syndrome. IL-18 showed good correlation with individual components of metabolic syndrome which was statistically significant.

- A strong association was seen between IL-18 and cerebrovascular accidents, cardiovascular outcomes and hypertension. The findings of this study indicate a utility of IL-18 as a prognostic marker in patients with metabolic syndrome. The possibility of IL-18 as a therapeutic target needs to be explored in further studies.

Chapter 8

Summary

SUMMARY

The metabolic syndrome (MetS) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a cluster of risk factors for CVD, including obesity, hypertension, elevated triglycerides and low levels of HDL Cholesterol. Interleukin-18 (IL-18), a recently described member of the IL-1 cytokine superfamily, is now recognized as an important regulator of innate and acquired immune responses. The present study was undertaken to study the association of IL-18 with metabolic syndrome and to correlate IL-18 levels with the different components of metabolic syndrome as well as its complications.

The present one year cross sectional study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 100 patients of metabolic syndrome based on IDF criteria specific for south Asians during the period of January 2010 to December 2010. Estimation of IL-18 was done using standard recombinant IL-18 enzyme linked immuno sorbent assay (ELISA) kit. Interleukin-18 levels above 216 pg/mL were considered as abnormal.

In the present study, males accounted for 64%. The mean age for the study population was 60.30 ± 9.43 years. Diabetes accounted for 71% as past history. 53% subjects were in the pre-obese group with a BMI between 25 to 29.99 kg/m^2. All the patients (100%) had abnormal WC. The mean fasting blood sugar level were 142 ± 28.8 mg/dL. 71 patients were found to have an elevated Il-18 level (71%) whereas 29 subjects had a IL-18 $\leq$ 215. Of the 100 patients

studied, 64% had three components, 29% had four and 7% had all five components of the metabolic syndrome. IL-18 was correlated with each of the components of the metabolic syndrome ($p<0.05$). On comparing the number of metabolic syndrome components with IL-18, a statistically significant association was observed with 37 subjects (57.8%) of patients with 3 components of the metabolic syndrome also having abnormal IL-18 levels. The strongest correlation of IL-18 was observed with HOMA-IR with a correlation coefficient of 0.646 ($p\leq0.001$). Fasting blood sugar levels ($\gamma=0.421$), insulin levels ($\gamma=0.403$), systolic blood sugar levels ($\gamma=0.364$), diastolic blood pressure ($\gamma=0.307$) showed definite, albeit weaker, associations with IL-18 which were all statistically significant ($p\leq0.001$).

Interleukin levels were found to be significantly higher in patients with metabolic syndrome. The findings of this study indicate a utility of IL-18 as a prognostic marker in patients with metabolic syndrome. The possibility of IL-18 as a therapeutic target needs to be explored in further studies.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Annexures

Annexure II

ANNEXURE II – PROFORMA

Case No:

NAME: AGE/SEX:

IP No. ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

HISTORY PERTAINING TO METABOLIC SYNDROME :

k/c/o Type 2 diabetes mellitus yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment –

Past history of cerebrovascular events –

Past history of angina pain/ Myocardial infarction/ Ischaemic heart disease or on any specific medication.

H/o peripheral neuropathy - yes ☐ no ☐

Documented Diabetic retinopathy/surgical management of retinopathy in the past

Diabetic nephropathy yes ☐ no ☐

Diabetic foot yes ☐ no ☐

Autonomic neuropathy yes ☐ no ☐

K/c/o Hypertension or on specific anti-hypertensive medication yes ☐ no ☐

H/o Peripheral vasucular disease/past h/o treatment for the same yes ☐ no ☐

K/c/o of dyslipidemia or on any specific medication yes ☐ no ☐

ON EXAMINATION :

- NUTRITION :

  HEIGHT :

  WEIGHT:

  BMI :

  WAIST CIRCUMFERENCE :

- BLOOD PRESSURE :

INVESTIGATIONS :

- FBS –
- TOTAL TRIGLYCERIDES –
- TOTAL HDL –
- TOTAL CHOLESTEROL-
- ESTIMATED LDL -
- HsCRP LEVELS –
- INTERLEUKIN 18 LEVELS –
- FASTING INSULIN LEVELS
- HOMA-IR –

ANNEXURE III - MASTER CHART

Sl. No.	IP No.	Age (Years)	Sex	T2 DM	HTN	CVA	CVD	PN	DR	BMI	WC	FBS	Cholesterol	LDL	TG	HDL	SBP (mm Hg)	DBP (mm Hg)	FIL	HOMA IR	CRP	IL-18
1	402311	58	M	+	+	-	-	-	-	27.89	95	116	165	36	146	18	138	90	31	12.50	11.1	201
2	402505	55	M	+	+	-	-	-	+	29.30	101	160	100	46	180	38	150	90	36	8.80	14.0	218
3	403376	65	M	+	+	-	+	-	+	30.82	98	144	110	36	214	31	140	90	39	10.49	17.1	252
4	403454	60	M	+	-	-	+	-	+	26.18	96	106	151	62	223	48	110	70	17	6.27	6.0	194
5	405981	60	F	+	+	+	-	-	-	30.89	98	176	150	54	202	24	156	90	36.8	13.49	16.0	246
6	405656	62	F	+	+	+	+	-	-	27.53	100	148	203	58	264	34	142	90	34.8	17.27	17.0	258
7	405493	58	M	-	+	+	-	-	-	24.67	94	98	160	36	154	52	158	100	22	8.60	8.0	196
8	405589	49	F	+	-	-	+	+	+	28.15	101	190	192	76	242	44	126	80	31	14.55	14.0	208
9	405816	50	M	+	+	+	+	-	+	30.42	106	204	106	53	91	35	154	90	40	10.36	21.0	294
10	404558	52	M	+	+	-	+	-	+	30.97	104	138	115	67	96	30	140	90	34	9.56	8.1	230
11	405254	45	F	-	+	-	-	-	-	26.29	90	110	132	46	160	52	140	90	20	6.45	10.0	190
12	404208	82	F	+	+	+	+	-	+	27.34	98	118	100	51	43	39	130	80	31	7.58	14.0	248
13	403730	76	M	+	+	+	+	-	-	30.45	102	176	150	90	153	35	138	90	28	10.27	16.0	256
14	404899	65	M	-	+	-	-	-	-	31.04	98	120	149	84	164	32	144	100	14	5.10	7.1	190
15	403026	64	M	+	+	+	+	-	+	31.77	110	216	200	80	192	26	150	100	38	18.58	20.0	277
16	405379	32	F	+	+	-	+	+	-	29.13	104	145	190	64	155	52	130	80	29	13.47	16.0	218
17	403847	59	M	+	+	-	-	-	+	30.01	106	140	150	70	165	40	156	90	24	8.80	12.0	196
18	405589	65	M	+	-	+	+	-	-	27.28	101	114	180	68	180	54	120	90	34	14.96	10.0	242
19	407599	62	F	+	+	+	+	+	+	33.20	120	230	170	90	233	30	138	100	38	15.79	22.0	306
20	408176	65	F	-	+	-	+	-	-	29.58	98	120	171	92	203	58	150	90	26	10.87	18.0	194
21	407746	60	F	-	+	-	-	-	-	28.47	96	88	294	95	195	59	150	90	31	22.28	20.0	232
22	408393	65	M	+	-	+	+	-	+	25.34	100	144	109	41	119	34	120	80	37.6	10.02	10.0	244
23	409483	48	F	-	+	-	+	-	-	25.91	101	124	202	104	282	30	140	90	56	27.65	12.0	316
24	409468	52	M	+	-	-	-	-	-	25.34	102	140	130	68	170	54	120	80	24	7.63	10.0	196
25	409548	52	M	+	+	-	+	-	-	29.30	109	162	197	59	185	26	140	90	33.2	15.99	14.0	238
26	410574	62	F	+	+	-	-	-	+	29.40	96	150	202	105	251	44	156	90	21	10.37	16.0	186
27	411261	69	M	+	+	+	+	-	-	30.44	98	126	150	97	154	30	160	90	38	13.93	18.0	296
28	411268	64	M	+	+	-	+	-	-	28.70	101	190	127	74	160	57	140	90	39.1	12.14	15.0	301
29	411810	55	M	+	+	-	-	-	+	30.40	110	128	124	68	75	41	136	86	24	7.27	16.0	198
30	411914	62	M	+	-	-	-	-	+	30.00	106	148	200	78	140	39	120	80	18	8.80	10.0	176
31	410767	60	M	+	-	+	+	-	+	30.48	108	126	190	56	71	36	110	70	30	13.93	12.0	219
32	412091	78	F	+	+	-	-	-	+	31.90	112	177	141	68	76	56	140	90	11.1	3.83	22.0	174
33	411941	48	M	+	-	+	+	-	+	27.30	98	186	221	120	208	44	120	80	40	21.61	21.0	320
34	412143	64	F	+	+	-	-	-	-	26.80	92	120	110	54	78	38	136	90	16	4.30	10.0	176
35	409488	71	M	-	+	-	+	-	-	29.06	101	106	203	38	160	48	138	100	26	12.90	13.0	218
36	409581	53	M	-	+	-	-	-	-	30.10	104	96	180	62	140	44	150	100	22	9.68	10.0	174
37	409781	64	F	+	+	+	+	+	+	33.70	118	164	203	64	200	30	160	100	56	27.79	28.0	400
38	409774	59	M	-	+	-	+	-	-	28.48	100	110	144	54	169	32	150	90	32	11.26	10.0	206
39	409929	55	M	+	-	-	-	-	-	27.04	98	136	176	70	100	34	110	70	20	8.60	8.0	166
40	409844	50	M	+	-	-	-	+	+	28.30	96	120	190	70	155	52	120	70	18	8.36	10.0	160
41	402201	44	F	-	+	-	+	-	-	30.17	104	112	184	76	180	34	150	100	34	15.29	16.0	284
42	402693	65	F	+	-	+	+	-	+	32.04	108	150	190	58	264	34	120	80	44	20.44	26.0	360
43	402593	70	M	+	+	-	+	-	+	27.45	103	124	140	50	190	55	140	90	38	13.00	24.0	219
44	402876	71	F	+	+	+	+	-	+	29.74	108	148	208	80	200	38	160	100	48	24.41	23.0	392
45	403171	43	M	-	+	-	-	-	-	29.92	98	118	130	60	156	48	150	90	22	6.99	16.0	194
46	403106	69	F	+	+	+	+	+	+	30.48	101	200	220	100	190	30	170	100	54	29.04	32.0	456
47	402834	51	M	+	-	-	+	+	+	38.37	106	155	225	90	210	23	120	70	39	21.45	20.0	301
48	403978	46	F	-	+	-	-	-	-	30.30	101	118	210	100	140	38	160	100	18	9.24	6.0	178
49	404210	64	M	+	-	+	-	+	+	26.58	98	156	196	56	154	60	120	70	36	17.25	18.0	238
50	404481	60	F	-	+	+	+	-	-	30.40	102	120	200	84	160	38	170	100	40	19.56	22.0	296
51	404375	61	M	+	+	-	+	+	+	29.71	101	138	166	88	155	55	140	90	38	15.42	19.0	277
52	404417	58	M	-	+	+	+	-	-	29.60	102	122	198	90	100	38	160	100	39	18.88	28.0	310
53	403552	55	M	+	-	-	-	-	+	28.12	104	140	244	66	155	56	110	70	21	12.53	8.0	168
54	405016	57	M	-	+	-	+	-	-	26.50	100	120	204	80	170	34	160	100	40	19.95	26.0	290
55	405981	60	F	+	+	+	+	-	+	32.13	104	210	230	86	204	32	150	90	46	25.86	30.0	362
56	405671	42	F	+	-	-	-	-	-	27.02	96	136	134	60	156	60	120	80	180	58.96	8.0	170
57	412997	70	M	+	+	-	+	-	+	30.30	106	148	200	78	168	44	140	90	36	17.60	24.0	262
58	413726	65	F	+	+	+	+	-	-	31.80	102	166	198	64	188	44	150	100	40	19.36	31.0	308
59	413721	56	M	+	-	+	+	-	-	29.80	104	144	218	90	166	34	120	80	48	25.58	20.0	388
60	413874	60	M	-	+	-	+	-	-	32.80	112	108	192	76	172	56	150	100	36	16.90	22.0	290
61	413371	70	F	+	+	-	+	-	-	28.7	98	176	154	60	146	38	150	100	31	11.67	21.0	266

ANNEXURE III - MASTER CHART

Sl. No.	IP No.	Age (Years)	Sex	T2 DM	HTN	CVA	CVD	PN	DR	BMI	WC	FBS	Cholesterol	LDL	TG	HDL	SBP (mm Hg)	DBP (mm Hg)	FIL	HOMA IR	CRP	IL-18
62	413539	67	M	+	+	+	+	-	+	30.8	106	144	198	90	151	40	140	90	42	20.33	26.0	360
63	413719	52	M	-	+	+	+	-	-	31.6	108	200	210	94	1712	42	140	90	41	21.05	29.0	394
64	416501	62	F	+	+	-	+	-	-	28.9	94	136	180	68	156	54	140	90	32	14.08	28.0	246
65	415830	62	F	+	+	-	-	-	-	27.27	92	146	156	60	146	44	150	100	12	4.58	8.0	162
66	415898	70	M	+	+	+	+	-	+	29.39	101	136	210	86	190	34	150	90	36	18.48	21.0	296
67	415922	56	M	-	+	+	+	-	-	30.01	108	108	218	90	160	42	160	100	42	22.38	32.0	306
68	415936	62	M	+	+	-	-	-	+	28.01	100	136	210	86	142	46	140	90	22	11.29	11.0	190
69	415997	56	M	+	+	-	+	-	+	27.67	98	146	200	67	156	56	140	90	29	14.18	19.0	218
70	416006	58	M	+	+	-	+	-	-	30.8	110	142	210	76	160	60	150	100	34	17.45	20.0	258
71	416025	60	M	-	+	+	-	-	-	28.8	98	110	150	60	140	32	150	90	31	11.37	15.0	232
72	4161633	66	F	-	+	-	-	-	-	27.9	96	101	180	68	150	50	140	90	12	5.28	8.0	180
73	416164	71	M	+	+	+	+	-	+	32.3	105	136	190	70	169	42	160	100	39	18.11	32.0	318
74	416147	50	M	+	-	-	+	+	+	29.3	99	138	190	88	146	52	130	60	32	14.86	18.0	256
75	416221	65	M	-	+	-	-	-	-	31.6	110	120	160	56	160	52	160	100	26	10.17	10.0	230
76	416486	62	F	+	+	+	-	+	+	30.8	104	150	180	70	146	46	140	90	33	14.52	26.0	244
77	416491	52	F	+	+	+	+	-	+	31.9	118	146	220	90	168	44	150	100	46	24.74	33.0	361
78	416605	58	M	-	+	-	+	-	-	27.8	96	130	178	89	160	54	140	90	33	14.36	22.0	240
79	416639	48	M	-	+	-	+	-	-	27.8	96	110	180	68	178	30	160	100	32	14.08	26.0	262
80	416682	52	F	+	+	-	-	-	+	26.9	96	146	150	56	130	56	150	90	20	7.33	11.0	170
81	416795	54	M	+	-	+	+	-	-	29.8	103	160	190	88	170	32	120	80	40	18.58	30.0	288
82	416897	70	M	-	+	-	+	-	-	29.01	101	110	190	76	176	30	160	100	36	16.72	26.0	284
83	416947	60	F	-	+	-	-	-	-	26.6	94	110	160	58	142	46	150	100	18	7.04	8.0	174
84	417027	60	F	+	+	+	+	+	+	32.8	112	160	256	96	176	36	160	90	46	28.79	30.0	401
85	417128	80	M	+	+	+	+	-	-	29.8	102	150	190	88	146	42	150	100	34	15.79	38.0	346
86	417218	68	M	+	-	-	-	-	+	37.8	100	160	200	60	208	36	120	80	19	9.29	22.0	216
87	416510	62	F	+	+	-	+	-	-	29.6	102	110	180	96	156	48	150	100	30	13.20	28.0	248
88	417227	46	M	+	-	+	-	-	-	28.9	101	160	200	106	218	36	130	80	40	19.56	38.0	296
89	417481	76	F	+	+	+	+	-	+	32.3	106	176	190	110	188	39	140	90	45	20.90	39.0	356
90	416398	65	M	+	+	+	+	+	+	32.6	108	168	290	148	190	36	170	100	57	40.41	48.0	406
91	417577	56	M	-	-	-	-	-	-	30.6	102	118	280	108	220	36	120	80	22	15.06	8.0	190
92	416636	80	M	-	+	+	+	-	-	31.6	106	120	190	60	166	52	160	100	41	19.04	36.0	310
93	417600	66	M	+	-	+	-	+	+	30.9	100	156	200	89	140	36	120	80	34	16.62	26.0	258
94	416467	58	F	+	+	-	+	-	-	27.1	94	190	200	96	166	38	150	100	31	15.16	27.0	251
95	417690	54	M	-	+	-	+	-	-	37.8	110	122	178	110	160	50	160	100	36	15.66	32.0	310
96	416131	50	M	+	-	-	-	-	+	26.6	94	136	180	64	141	44	120	70	20	8.80	9.0	188
97	417361	77	M	-	+	+	+	-	-	30.8	100	112	200	98	198	36	180	100	44	21.51	38.0	318
98	417409	49	M	+	+	+	-	-	-	30	104	156	180	86	166	38	150	100	41	18.04	40.0	301
99	416418	78	M	+	+	+	+	-	+	32.8	110	176	240	121	180	41	100	100	52	30.51	40.0	410
100	417421	80	F	+	+	+	+	-	+	31	98	150	220	106	158	32	140	90	42	22.59	36.0	396

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

BMI	– Body mass index
BP	– Blood pressure
Cholesterol	– Total Cholesterol
CVA	– Cerebrovascular accidents
CVD	– Cardiovascular disease
Dias	– Diastolic blood pressure
DR	– Diabetic retinopathy
FBS	– Fasting blood sugar
FIL	– Fasting insulin levels
HDL	– High density lipoproteins
HOMA-IR	– Homeostatic model assessment – Insulin resistance
hsCRP	–Highly sensitive C-reactive protein
HTN	– Hypertension
IL-18	– Interleukin 18
IP no.	– In-Patient number
LDL	– Low density Lipoprotein
PN	– Peripheral neuropathy
Sys	– Systolic blood pressure
T2DM	– Type 2 diabetes mellitus
TG	– Triglycerides
WC	– Waist circumference