"TO STUDY THE CORRELATION OF URINE MELATONIN WITH METABOLIC SYNDROME AND ITS MANIFESTATION AT TERTIARY CARE HOSPITAL- A CROSS SECTIONAL STUDY"

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
MetS	Metabolic Syndrome
BP	Blood Pressure
HDL	High-Density Lipoprotein
CVD	Cardiovascular Diseases
IDF	International Diabetes Federation
IR	Insulin Resistance
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
BMI	Body Mass Index
WHR	Waist-Hip Ratio
FBG	Fasting Blood Glucose
AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
LDL	Low-Density Lipoprotein
PCOS	Polycystic Ovary Syndrome
FFAs	Free Fatty Acids
NAFLD	Non-Alcoholic Fatty Liver Disease
IL-6	Interleukin-6
TNFα	Tumor Necrosis Factor-alpha
CRP	C-Reactive Protein
TLRs	Toll-Like Receptors

aMT6S	6-Sulfatoxymelatonin
6-OMS	6-Oxymelatonin Sulfate
OGTT	Oral Glucose Tolerance Test
HbA1c	Glycated Hemoglobin
MT	Melatonin
WC	Waist Circumference
J.N. Medical College	Jawaharlal Nehru Medical College
SAEs	Serious Adverse Events
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
IQR	Interquartile Range
FBS	Fasting Blood Sugar
PPBS	Postprandial Blood Sugar
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
HTN	Hypertension
IHD	Ischemic Heart Disease
ELISA	Enzyme-Linked Immunosorbent Assay

ABSTRACT

Background:

Metabolic Syndrome (MetS) is a cluster of conditions, including obesity, hypertension, dyslipidaemia, and hyperglycaemia, linked to cardiovascular diseases and type 2 diabetes. Melatonin, a hormone regulating sleep, has antioxidant and metabolic regulatory properties. Urinary melatonin levels are a non-invasive biomarker for melatonin production. This study explored the relationship between urinary melatonin levels and MetS in an Indian population with high MetS prevalence and limited melatonin research.

Methods:

A cross-sectional study was conducted at a tertiary care hospital in Belagavi, India (2023–2024). It included 120 MetS patients (NCEP ATP III criteria). Assessments included urinary melatonin, blood glucose, lipid profiles, blood pressure, and anthropometrics. Data were analyzed using SPSS and R software.

Results:

Among 120 participants (mean age: 58.23 ± 12.6 years; 68.33% male), 74.17% fell into obesity classes 1 and 2, 85.83% were hypertensive, 71.67% had low HDL, and 85% were diabetic. Abnormal urinary melatonin levels were found in 41.8%. Hypertension was higher in the abnormal melatonin group (93.88%) vs. normal (80.28%) ($p = 0.0358$). No significant correlations were found between melatonin and other MetS components ($p > 0.05$).

Conclusion:

Abnormal urinary melatonin levels were linked to hypertension but not other MetS components. The lack of significant correlations between urine melatonin levels and other variables suggests that melatonin levels may not be strongly influenced by these factors. However, the association with hypertension needs further investigation to understand the underlying mechanisms and potential implications for cardiovascular health

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Metabolic syndrome (MetS) term was first given in 1975 by Haller and Hanefeld. MetS includes obesity, increased blood pressure (BP), dyslipidaemia, hyperglycaemia and decreased levels of high density lipoprotein (HDL) cholesterol. The combination of all these risk factors contributes to cardiovascular diseases (CVD), type 2 diabetes , and other complications like stroke and non-alcoholic fatty liver disease .[1,2] NCEP ATP III defines MetS as when an individual meets at least three of these five criteria: a waist circumference of more than 40 inches and of 35 inches for men and women, respectively, BP of more than 130/85 mmHg, fasting triglyceride levels of more than 150 mg/dL, HDL cholesterol levels below 40 mg/dL or 50 mg/dL for men and women respectively, and fasting blood sugar levels greater than 100 mg/dL. New criteria was published by International Diabetes Foundation (IDF) for MetS in 2005, which was similar to the NCEP ATP III criteria, consider that the presence of obesity as important parameter for diagnosis, though Insulin Resistance (IR) is not a mandatory requirement.[2–4]

The global prevalence of MetS is 25% as given by IDF .[5] A meta-analysis was conducted in 2022 according to which prevalence of MetS is ranging from 12.5% to 31.4%. In the Eastern Mediterranean Region and the Americans the prevalence was higher which showed a positive correlation with a country's income level. Among individual components of MetS, the global prevalence was highest for ethnic-specific central obesity at 45.1%, followed by elevated blood pressure at 42.6%. Low HDL cholesterol levels had a prevalence of 40.2%. Elevated serum triglycerides were observed in 28.9% of participants, and 24.5% had fasting plasma glucose, levels of ≥5.6 mmol/L.[6]

Systematic review and meta-analysis conducted for Indian population has reported that the prevalence of MetS at 30%, ranging from 13% in the 18–29 age group to 50% in those aged 50–59 years.[7] In a study from Kanpur, the prevalence of MetS was found to be over 40%.[8] Another study reported a MetS prevalence of 37.65%.[9] Studies which was conducted in South Indian population gives prevalence rates of 22.1% to 41%.[10–12] Similarly, a northern Indian study reported a prevalence rate of 22.37%.[13] Prevalence of MetS in a study which was conducted from eastern coastal india was found to be 43.2%.[14]

Melatonin is a hormone secreted by pineal gland, is primarily known for regulating the sleep-wake cycle.[15] It also maintains metabolic health by acting as an antioxidant and anti-inflammatory agent.[16] Melatonin enhances insulin sensitivity, improves glucose metabolism, and modulates lipid profiles by decreasing triglycerides and cholesterol levels.[17] These effects, combined with its antioxidant properties, help protect cells from oxidative damage and promote overall metabolic balance.[18] Low melatonin levels are also linked to poor sleep quality, which may contribute to components of MetS. Sleep disturbances, that causes disruption in the circadian rhythm, can lead to ,an imbalance in metabolism.[19,20]

Urinary melatonin has emerged as a reliable and non-invasive biomarker for assessing systemic melatonin levels, providing insights into individual melatonin production and circadian rhythm integrity.[21] Investigating melatonin levels in patients with MetS can shed light on the pathophysiological mechanisms underlying this condition, as disruptions in melatonin secretion may be linked to metabolic abnormalities.[18,22] These urinary levels can effectively serve for early detection, risk stratification, and monitoring of the progression of MetS. By assessing melatonin levels, healthcare professionals can evaluate the impact of various interventions—

such as lifestyle modifications and pharmacological treatments—on metabolic health, optimising treatment strategies and improving patient outcomes.

Most studies exploring the link between melatonin and MetS have focused on deranged melatonin levels as a marker for the development of the syndrome, primarily in animal models, including rats. These studies typically assess melatonin concentrations in serum and plasma rather than urine. There is limited study of melatonin in the context of MetS, especially in Indian cohorts. While much of the existing literature on melatonin's role in MetS has been conducted in Western populations, there is limited research on this topic within the Indian demographic. Given the unique genetic predispositions, dietary practices, and high prevalence of MetS risk factors in India, conducting this study in an Indian population is necessary.

This study investigated the relationship between urinary melatonin levels and the clinical manifestations of MetS in patients at an Indian tertiary care hospital. By focusing on this specific cohort, the research evaluated the potential of urinary melatonin as a biomarker for MetS and its associated complications. The findings aimed to enhance understanding of melatonin's role in the pathophysiology of MetS, informing the development of targeted interventions. Additionally, the study sought to contribute to culturally appropriate prevention and treatment strategies for MetS in India, where the condition is highly prevalent. Ultimately, this research aimed to improve public health efforts and clinical practices by advancing knowledge of melatonin's role in metabolic health within the Indian population.

AIMS AND OBJECTIVES

To establish whether deranged melatonin level is a marker for development of Metabolic Syndrome.

REVIEW OF LITERATURE

The concept of MetS was first introduced by Gerald Reaven (1988), who termed it "syndrome X" to describe a constellation of cardiovascular risk factors occurring simultaneously in the same individual.[1,23] The condition was referred to by various names, including "the deadly quartet" by Kaplan and "a silent killer" by Foster.[24,25] Given that IR was identified as the underlying pathophysiological mechanism, Haffner et al. gave the term "IR syndrome". The term "MetS" has become the most widely accepted for the aggregation of metabolic abnormalities. Dr. Vague's early observations identified that central (abdominal) obesity, particularly in the upper body, was associated with a greater number of metabolic disturbances. The defining metabolic abnormalities of MetS include IR, impaired glucose tolerance, central obesity, dyslipidaemia, and hypertension.[25,26]

The World Health Organization (WHO) diabetes consultation group established the first internationally accepted definition of MetS in 1998.[2]

Diagnostic criteria for MetS: MetS is defined and diagnosed according to several international organisations, each having its own criteria.

World Health Organization Criteria (1998)[27]: A diagnosis requires the presence of T2DM, FBG above 100 mg/dL, or impaired glucose tolerance (IGT), along with at least two of the following conditions:

- A WHR >0.9 for men or 0.85 for women or BMI over 30 kg/m².
- Triglyceride levels ≥ 150 mg/dL /or HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women.
- BP ≥ 140/90 mmHg.

- Urinary albumin excretion of at least 20 μg/min or an albumin-to-creatinine ratio of 30 mg/g or greater.

European Group for the Study of IR Criteria (1999)[28]**:** IR is identified when insulin levels > the 75th percentile among non-diabetic individuals and is accompanied by at least two of the conditions:

- Waist circumference ≥ 94 cm (men) or ≥ 80 cm (women).
- Triglycerides ≥ 150 mg/dL or HDL < 39 mg/dL (both men & women).
- BP ≥ 140/90 mmHg or on antihypertensives.
- FBG ≥ 110 mg/dL.

NCEP: ATPIII Criteria (2001)[29]**: P**resence of at least three of these criteria confirms diagnosis:

- Waist circumference > 102 cm (men) or > 88 cm (women).
- Triglycerides ≥ 150 mg/dL.
- HDL < 40 mg/dL (men) or < 50 mg/dL (women).
- BP ≥ 130/85 mmHg.
- FBG ≥ 110 mg/dL; revised to ≥ 100 mg/dL (ADA, 2003).

American Association of Clinical Endocrinology Criteria (2003)[30]**:** A diagnosis requires the presence of IGT along with at least two of the following conditions:

- BMI ≥ 25 kg/m².
- Triglycerides ≥ 150 mg/dL and/or HDL < 40 mg/dL (men) or < 50 mg/dL (women).
- BP ≥ 130/85 mmHg.

International Diabetes Federation (IDF) Criteria (2005)[26]**:** A diagnosis requires central obesity, determined by waist circumference along with at least two of the following criteria:

- Triglyceride levels of 150 mg/dL or higher.
- HDL cholesterol levels below 40 mg/dL in men and below 50 mg/dL in women.
- Blood pressure readings of 130/85 mmHg or greater.
- Fasting glucose levels of 100 mg/dL or higher.

American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) Criteria (2004)[31]**:** At least three of the conditions to be present:

- Waist circumference ≥ 102 cm (men) or ≥ 88 cm (women).
- Triglycerides ≥ 150 mg/dL.
- HDL < 40 mg/dL (men) or < 50 mg/dL (women).
- BP ≥ 130/85 mmHg.
- FBG ≥ 100 mg/dL.

Prevalence of MetS

A study by Krishnamoorthy et al. estimated the prevalence of MetS it revealed a pooled prevalence of MetS in India at 30%. Urban populations had a higher prevalence (32%) compared to tribal (28%) and rural populations (22%). Gender-wise, females exhibited a higher prevalence (35%) compared to males (26%). This study highlights that nearly one in three adults in India are affected by MetS, with variations observed based on demographic and geographic factors.[7]

A study by Ramachandran et al. included 475 participants aged 20–75 years. The study found that 41.1% of participants had MetS, 31 % had increased WC, 46% had high TG, 65.5% had low HDL, 55.4 % had hypertension, and 26.7% had elevated FPG. Prevalence of MetS was higher in women than men (46.5% vs. 36.4%, p=0.03), and prevalence increased with age.[11]

A study by Khan et al. among 420 participants reported that 172 individuals (40.9%) were diagnosed with MetS, with females (59%) compared to males (26.2%). The prevalence was higher in > 50 years (31.9%). Hyperglycaemia was the most common abnormality, present in 29.2% of the total population, with females exhibiting higher rates of hyperglycaemia, obesity, and elevated triglycerides. Among those diagnosed with MetS, hyperglycaemia was the most prevalent factor (71.5%), while males had higher rates of hypertension and low HDL levels.[8]

A study conducted by Sinha et al. in Kanpur reported the prevalence of MetS as 38%. It was more prevalent in older population (60.3 ± 8.4 years) and females (35.24%).[9]

A study in Chandigarh, India by Ravikiran et al. determined the prevalence and risk factors for MetS among 2,225 participants. The results showed a prevalence of 35.8%, 45.3%, and 39.5% based on NCEP ATP III, modified NCEP ATP III, IDF criteria respectively. Central obesity was common among females, while elevated BP was more common in males.[13]

A study by Wasir et al. in North India among 2050 subjects reported prevalence of MetS as 49.2%. It also identified a high prevalence of other MetS components, such as hypertension, high BMI, hypertriglyceridemia, and low HDL-C,

even in those without abdominal obesity. The study found that more cases can be detected by making WC a non-obligatory criterion and including BMI.[32]

Risk Factors for MetS

A. Modifiable Risk Factors

Factors that can be altered through changes in the person's lifestyle, medical interventions, or by taking other preventive measures.

1. **Obesity and Central Adiposity:** The excessive accumulation of visceral fat is linked to the onset of IR, inflammation, and the dysregulation of adipokines, all of which contribute to various metabolic abnormalities.[33] Central obesity exacerbates lipid dysregulation, characterised by increased TG levels, reduced HDL cholesterol, increased BP and impaired glucose tolerance. Visceral fat is not merely a passive storage depot but an active endocrine organ. It releases free fatty acids and inflammatory cytokines that can disrupt insulin signalling pathways, thereby increasing the risk of cardiovascular disease.[34]

2. **Dietary Habits**: The consumption of out-of-home meals and energy-dense fast foods,[35] along with snacks containing highly processed meats, saturated and trans-fatty acids, refined carbohydrates, and sodium, has been linked to postprandial metabolic disturbances.[36] These disturbances include dyslipidaemia, subclinical inflammation, and oxidative stress. They contribute to elevated fasting insulin levels, a key driver of IR, ultimately increasing the risk of developing MetS in adults.[37,38]

3. **Sedentary Lifestyle** Physical inactivity, commonly characterised by the absence of moderate or vigorous physical activity[39], along with sedentary

behaviour[40], has been identified as a risk factor for MetS. According to a study, individuals with MetS spend more sedentary time (67%) than those without MetS (62%), with difference being statistically significant. They also have longer sedentary bouts (18 min) than those without MetS (17 min) and took fewer breaks from sedentary behaviour ($P < 0.01$). The study concluded that even after controlling for factors such as age, sex, alcohol consumption, smoking, BMI, diabetes, heart disease, and physical activity, a higher percentage of sedentary time and fewer sedentary breaks were significantly associated with a greater likelihood of MetS.[41]

4. **Smoking**: Cigarette smokers face a increased risk of developing MetS due to the direct and indirect effects of smoking on its diagnostic components. Studies indicate that smoking adversely impacts obesity-related measures, BP, blood glucose levels, and lipid profiles.[42] A meta-analysis by Sun et al. found that smokers are 1.26 times more likely to develop MetS compared to non-smokers, with the risk increasing further to 1.42 among heavy smokers (defined as those smoking 20 cigarettes per day).[43]

5. **Sleep Disorders**: Several studies have investigated the relationship between sleep disorders and MetS. A study reported a significant association between insomnia and MetS. Zou et al. conducted a study in Sweden among 830 adults between 50–64 years. The findings revealed that lack of sleep independently increased the risk of MetS (OR = 1.97). When pthey compared adults with insomnia and without, they found that individuals with insomnia had lower HDL cholesterol levels and higher TG levels.[44] In another study among larger sample size with age 35 years and above conducted in Taiwanese, they found that even after controlling sleep duration insomnia symptoms significantly

increased the likelihood of meeting each MetS criterion including high WC, low HDL cholesterol, increased LDL cholesterol, TG levels, and fasting plasma glucose.[44,45]

B. Non-Modifiable Risk Factors

Non-modifiable factors are intrinsic characteristics that cannot be altered but help predict the risk of MetS.

1. **Genetics and Family History**: A history of T2DM in the family, hypertension, or dyslipidaemia increases susceptibility to MetS. Families with a positive history of MetS have shown a significantly higher susceptibility to developing MetS compared to families without a history of the condition (42.63%).[46] Chiu et al. investigated the link between history of diabetes in the family and MetS in a cohort of 5000 participants from the Taiwan Biobank. They conducted the regression analysis and found that participants with a sibling FH of diabetes, parental FH of diabetes, and simultaneous sibling and parental FH of diabetes had significantly higher odds of MetS, i.e 1.8, 1,7, 2.9 ($p =<0.001$).[47]

2. **Age**: Age is contributing factor for MetS, as physiological changes such as decreased metabolic rate and increased body fat occur with ageing. These changes often lead to IR, hypertension, and dyslipidaemia. Additionally, lifestyle factors, including reduced physical activity and dietary shifts, further heighten the risk. A study conducted in Bangladesh reported that the prevalence of MetS and its components increased with age. Regression analysis demonstrated association between advancing age and a higher risk of MetS in both students and academic staff ($p < 0.05$).[48]

3. **Ethnicity**: Among women, the highest prevalence of MetS was found in Asians (41.2%), while the lowest was in Black/African women (26.7%).[49] A review reported that abdominal obesity is particularly prevalent among South Asians. It highlighted that even with similar BMI levels and lower average waist circumference compared to Caucasians, South Asians still experience higher body fat, abdominal adiposity, and cardiovascular risk.[50]

4. **Sex Differences**: Recently, MetS has been more prevalent in men than in women. Estrogen and testosterone directly influence glucose and lipid metabolism, with lower estrogen levels or a relative increase in testosterone contributing to IR and a more atherogenic lipid profile. Hypertension remains a key risk factor for MetS in both sexes, although its prevalence increases more rapidly in women with age. Menopause and polycystic ovary syndrome (PCOS) are also significant contributors to the development of MetS due to the effects of sex hormones.[51]

C. Hormonal Influences in MetS:

Hormonal dysregulation significantly contributes to MetS (MetS), affecting IR, lipid metabolism, and fat distribution. IR promotes hyperinsulinemia, glucose intolerance, and increased visceral fat. Adipokines like leptin and adiponectin influence appetite and metabolism, with leptin resistance and low adiponectin levels worsening IR and inflammation. Sex hormones also play a role: oestrogen in premenopausal women helps regulate fat distribution, while its decline after menopause shifts fat to the abdomen, increasing MetS risk. Elevated androgens in women with conditions like PCOS are linked to obesity and IR, while low testosterone in men contributes to visceral fat. Chronic stress increases cortisol,

promoting abdominal fat and glucose issues. Hypothyroidism and growth hormone deficiencies are also associated with MetS, contributing to weight gain and IR.[52]

Pathophysiology of MetS

MetS develops from interactions between genetic, environmental, and lifestyle factors, like poor diet and inactivity. Excessive caloric intake, particularly leading to abdominal fat accumulation, is a key trigger for MetS.[53,54] The primary contributors to MetS include IR, chronic inflammation, and neurohormonal disturbances, which ultimately increase the risk for CVD and T2DM.

Insulin Resistance: IR impairs glucose and lipid metabolism. In adipose tissue, IR prevents fat breakdown, leading to elevated free fatty acids (FFAs) in circulation. These FFAs interfere with insulin signalling, decreasing glucose uptake in muscles and stimulating glucose production in the liver. Over time, this results in beta-cell dysfunction and increased risk for MetS, contributing to hypertension, dyslipidaemia, and atherosclerosis.[55–57]

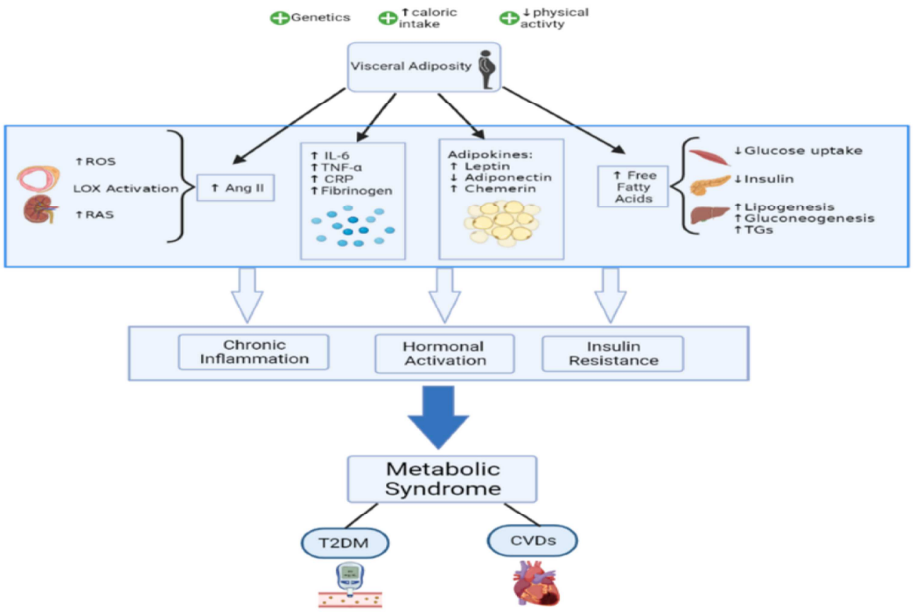

Figure 1: Pathophysiology of MetS[58]

Adipose Tissue: Adipose tissue also acts as an endocrine organ releasing hormones leptin and adiponectin. In obesity, leptin resistance disrupts metabolism, while low adiponectin levels are associated with IR and inflammation. Elevated chemerin levels also correlate with MetS. In obesity and IR, the renin angiotensin system is activated and contributes to oxidative stress, endothelial dysfunction, and vascular damage, exacerbating MetS.[58–60]

Chronic Inflammation: Chronic inflammation is central to MetS. Elevated inflammatory markers like IL-6, TNFα, and CRP are linked to IR and increased cardiovascular risk. IL-6 and TNFα from adipose tissue impair insulin signalling and increase FFAs, worsening metabolic dysfunction.[61] Additionally, the activation of Toll-like receptors (TLRs) in response to fatty acids and oxidised LDL triggers inflammation, contributing to MetS. Gut microbiota disturbances also appear to play a role by increasing intestinal permeability, allowing endotoxins to activate TLR4 and further promote inflammation.[62]

Role of Melatonin in MetS

a. Melatonin Physiology and Production of Melatonin: Melatonin is a hormone predominantly synthesised in the pineal gland. Its production is regulated by the body's circadian rhythms, with synthesis being stimulated by darkness and suppressed by light exposure.[63] The amino acid tryptophan is converted into serotonin which is subsequently converted into melatonin through a series of enzymatic reactions involving tryptophan hydroxylase, aromatic L-amino acid decarboxylase, and N-acetyltransferase. The rhythmic production of melatonin follows the light-dark cycle, peaking during the night and reaching its lowest levels during daylight hours. Melatonin also functions as an antioxidant by removing free radicals and protecting

cells from oxidative damage. This dual function of melatonin, regulating sleep and offering antioxidant defence, is crucial for maintaining overall homeostasis.[64]

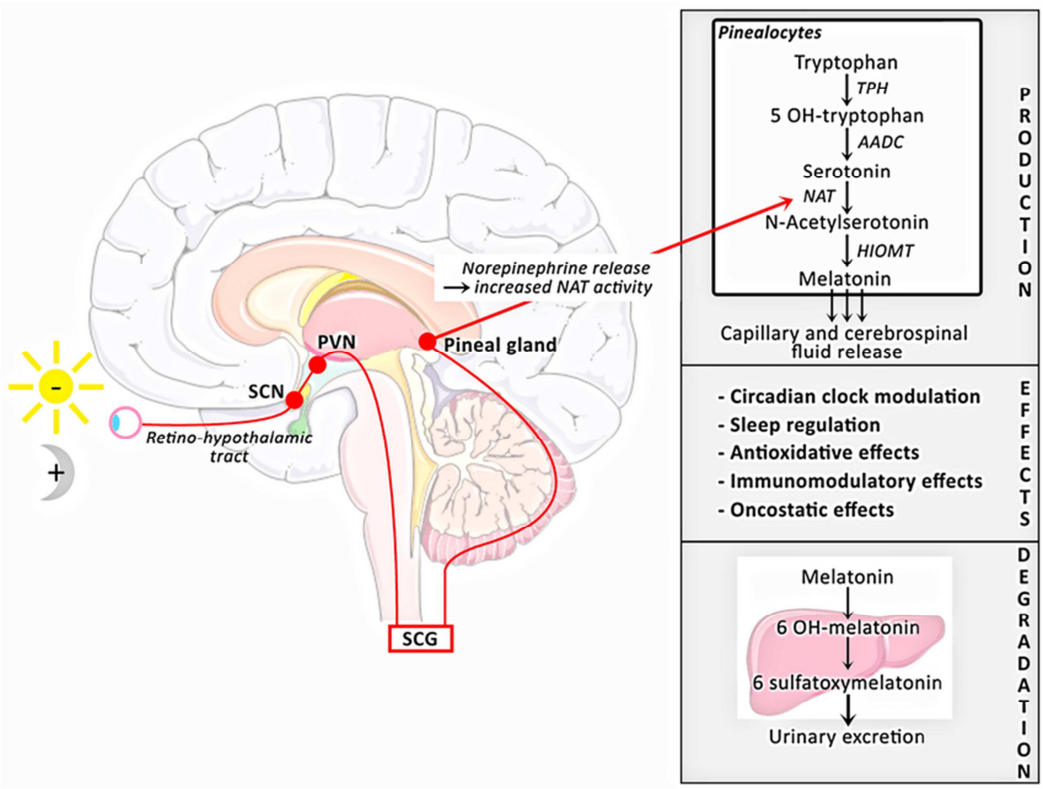

Figure 2: Melatonin synthesis and secretion by the pineal gland[65]

b. Melatonin and Metabolic Regulation: Melatonin improves insulin sensitivity, facilitating glucose uptake by peripheral tissues, which helps protect against IR.[66] Additionally, melatonin has significant effects on lipid metabolism, including modulating the activity of enzymes involved in both fat oxidation and storage.[67] It is also involved in the regulation of appetite through its influence on leptin and ghrelin hormones, which are central to the regulation of hunger and satiety.[68] Irregular sleep patterns can disrupt circadian rhythm and can lead to metabolic disturbances as these are often associated with increased risks of obesity, T2DM, and CVD.[69,70] Melatonin synchronises these rhythms and thus plays a protective role in maintaining metabolic health.[71]

c. Urinary Melatonin as a Biomarker: Urinary melatonin, particularly its main metabolite 6-sulfatoxymelatonin (aMT6S), has been identified as a valuable biomarker for assessing the function of melatonin secretion and its disruption in various health conditions, including MetS.[72] Urinary excretion of melatonin is a non invasive method. Abnormal urinary melatonin levels have been associated with obesity, IR, and dyslipidaemia. Melatonin levels are reduced in diseases associated with IR, like MetS.[19]

The measurement of melatonin levels in urine can provide insights into the synchronisation of circadian rhythms and metabolic disturbances. Furthermore, monitoring urinary melatonin may help clinicians and researchers track the impact of lifestyle factors, such as sleep duration and light exposure, on metabolic health. This approach could also offer a method for evaluating the efficacy of interventions aimed at correcting circadian misalignment and improving metabolic function.

Manifestations of MetS

Signs and symptoms of MetS include a range of clinical features that reflect underlying metabolic dysfunction. Central obesity, also known as visceral or apple-shaped adiposity, is a key indicator and involves excessive fat accumulation around the abdominal region and trunk. This type of fat distribution is strongly linked to IR and cardiovascular risks. MetS is also characterised by high BP, reduced levels of HDL cholesterol, elevated fasting serum TG, and impaired fasting glucose or IR, which may progress to prediabetes or T2DM.[73]

Additionally, MetS is often associated conditions like hyperuricemia, or elevated uric acid levels, can lead to gout and is commonly observed. Fatty liver disease, particularly NAFLD, is frequently present and can progress to severe liver

damage. Polycystic ovarian syndrome (PCOS) is a related condition in women, causing hormonal imbalances and irregular menstrual cycles. In men, MetS may present as erectile dysfunction due to vascular and hormonal changes. Acanthosis nigricans, dark velvety patches of skin commonly found on the neck, armpits, or groin, is another visible sign linked to IR.[73]

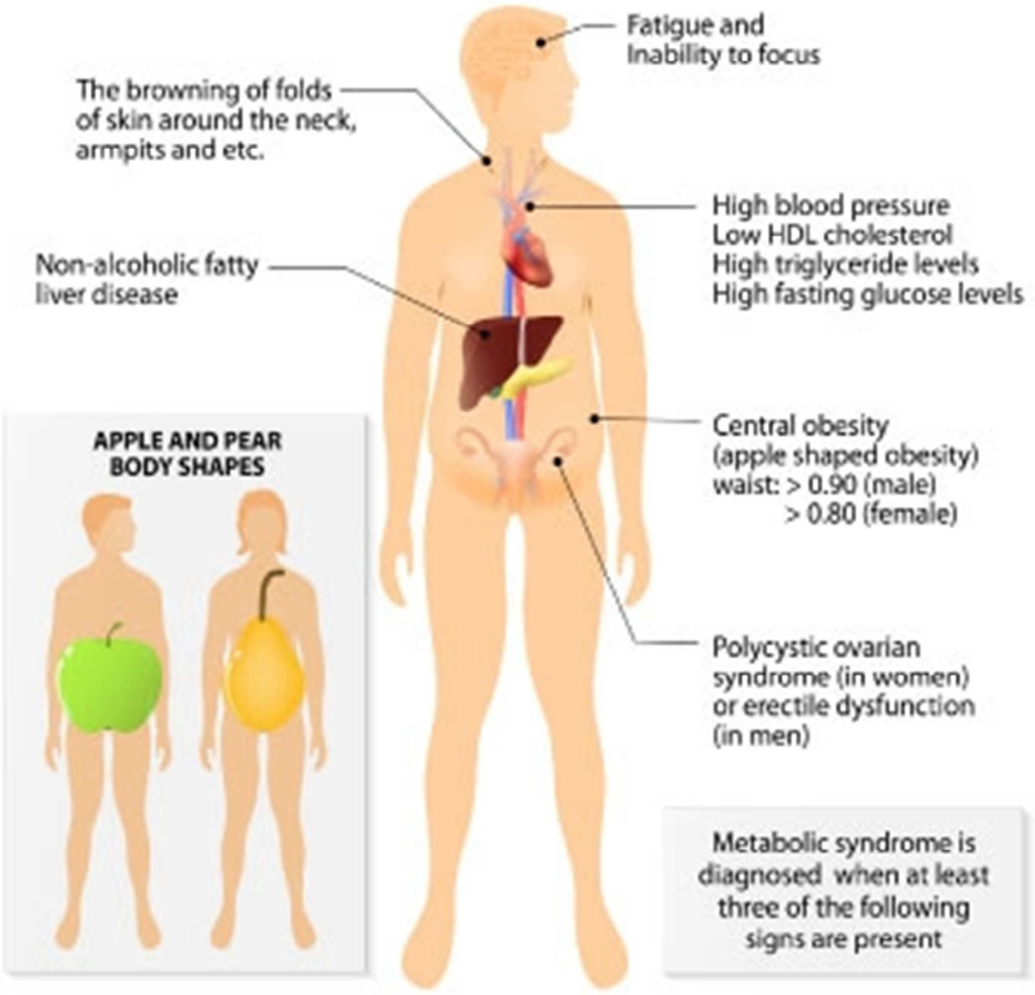

Figure 3: Symptoms of MetS[74]

Review of Studies Conducted on Similar Topics

The study by Balliuzek et al. found that patients with MetS exhibited elevated levels of 6-oxy melatonin sulfate, the main metabolite of melatonin, in their morning urine samples, indicating increased melatonin production at night. Even though melatonin decreases with age, this trend was observed even in older patients. The study also highlights that the correlation between melatonin hypersecretion and MetS symptoms depends on the patient's age. Melatonin levels could thus be used as a biological marker and prognostic factor for the progression of MetS.[75]

A study was conducted among 25 men with MetS and compared them to 23 healthy controls. This study investigates the link between melatonin, leptin, and insulin secretion. Melatonin secretion was measured by 6-oxymelatonin sulfate (6-OMS) levels in urine samples collected at 4 a.m. The results showed that melatonin secretion increased in both groups but was lower in MetS patients. A moderate negative correlation was found between 6-OMS levels and plasma insulin and glucose levels. Additionally, 6-OMS levels had a strong negative correlation with leptin levels. Multiple regression analysis revealed strong linear relationships between 6-OMS and both insulin ($r = 0.93$) and leptin levels ($r = 0.95$). The study also found that patients with a peakless melatonin secretion profile had a threefold increased risk of IR compared to controls (OR = 3.0).[76]

The study by Robeva et al. aimed to investigate the relationship between melatonin in young men with MetS (MS). The results showed no changes in melatonin concentrations between the two groups, indicating that melatonin secretion remained unimpaired in MetS patients.[77] Another study by Robeva et al. found that melatonin and insulin ratio (night time) was negatively correlated with LDL cholesterol and total cholesterol and positively correlated with HDL cholesterol

levels. Night-time melatonin levels were also positively correlated with night-time insulin concentrations, a relationship that was more pronounced in MetS patients. In MetS patients, there was negative correlation between the difference in melatonin in day and night with fasting glucose and positively with daily insulin levels.[78]

The study by Reutrakul et al. was conducted among 62 prediabetes patients, it aimed to assess the link between nocturnal urinary 6-sulfatoxymelatonin and glucose metabolism. The results showed that higher nocturnal urinary aMT6s levels were significantly associated with lower fasting insulin, lower IR and better insulin sensitivity. However, aMT6s levels were not correlated with fasting glucose, glucose response to the oral glucose tolerance test (OGTT), or HbA1c. After adjusting for BMI, the correlation between higher aMT6s levels and lower IR remained significant.[79]

The study by Mahmood and Hilal included 60 male MetS patients (aged 18–50) and 30 healthy controls. Blood samples were collected between 10 P.M. and 1 A.M. to measure serum melatonin, HbA1c, and lipid profiles. Results showed significantly lower melatonin levels in MetS patients (206.55 ± 105 pg/ml) compared to controls (298.82 ± 110.4 pg/ml). Additionally, MetS patients exhibited significantly elevated HbA1c levels and lipid profiles ($p < 0.001$). The findings suggest that reduced melatonin levels, alongside poor glycemic control and abnormal lipid profiles, may contribute to the progression of MetS.[80]

The study by Corbalán-Tutau et al. investigated the relationship between melatonin and components of MetS In 70 women (30 without MetS and 40 with MetS). Salivary melatonin was measured before lunch (14:00) and at night (03:00). Results showed significantly lower nocturnal melatonin levels in women with MetS compared to those without. Melatonin night/morning ratios were positively correlated

and associated with MetS scores and its components. A diminished amplitude in daily MT was linked to metabolic disturbances, including abnormalities in blood pressure, glucose, lipid regulation, and hormone levels such as ghrelin, leptin, and adiponectin.[81]

Bayon et al. conducted a study which showed significant interactions between gender and work schedules in relation to MetS, high TG, and visceral obesity. Prevalence of MetS was higher in men working permanent night shifts due to visceral obesity. Also, compared to permanent day workers, women on night shifts had an increased risk of high TG.[82]

Al-Sarraf et al. carried out a cross-sectional study among 28 healthy normoglycemic individuals, 29 with MetS but normoglycemic, and 30 with MetS (pre-diabetic/diabetic). The results showed significantly higher Melatonin levels in the MetS group. These were positively correlated with the WC, atherogenicity index of plasma, and systolic BP ($p < 0.05$). Melatonin levels were inversely correlated with HDL.[83]

MATERIALS AND METHODS

Study Setting: The Medicine Ward of a tertiary care hospital, J.N. Medical College, Belagavi.

Study Design: Hospital-based, cross-sectional study

Study Period: Two years, from February 1, 2023, to December 31, 2024.

Study Population: Patients with MetS visiting the hospital.

Sample Size:

Sample size (n) calculation formula:

$$N = \frac{Z^2 \times P \times (1-P)}{d^2}$$

Where:

- n = required sample size
- Z = standard normal variate
- P = prevalence
- d = margin of error or desired precision (8%)

Taking prevalence from a cross-sectional by Vasan et al. in southern India (22.1%).[12]

$$= \frac{(1.96)^2 \times 0.221 \times 0.779}{0.08 \times 0.08}$$

= 0.661 / 0.0064 = 104

Adjustment for dropouts/non-responses (20% increase): 120

Sampling Technique: A universal sampling technique was used to select the participants for this study. Every year in hospital, approximately 120 patients are diagnosed with MetS.

Inclusion Criteria: The study included patients who were diagnosed with MetS according to NCEP ATP III criteria.[84] MetS was considered present if three or more of the following five criteria were met:

- Waist more than 40 inches or 35 inches for men and women respectively
- BP readings ≥ 130/85 mmHg or higher.
- Fasting triglyceride levels > 150 mg/dL.
- HDL cholesterol levels < 40 mg/dL for men or < 50 mg/dL for women.
- Fasting blood glucose (FBG) levels >100 mg/dL.

Exclusion Criteria: Patients were excluded from the study if they had the following conditions:

- Tuberculosis
- Cancer
- Other hormonal disorders
- Patients on antiretroviral therapy (ART), anti-tuberculosis (AKT) drugs, chemotherapy, or hormone replacement therapy (HRT)
- Renal disorders
- Patients using melatonin supplements
- Patients on antipsychotic drugs

Variables used in the study: Urinary melatonin levels, FBG levels, postprandial blood glucose levels, total cholesterol, triglycerides, HDL cholesterol, body mass index (BMI), waist-to-hip ratio (WHR), BP.

Method of data collection: This cross sectional study was conducted in the tertiary care centre in Belagavi. Before enrolment informed consent was taken from all study participants, ensuring they understood the purpose, procedures, and potential risks related to the study. MetS was diagnosed using the NCEP ATP III criteria. Patients meeting the inclusion criteria underwent a series of clinical and laboratory assessments to measure various parameters related to MetS and melatonin levels.

Midstream urine samples (15 mL) were collected from each participant in the morning to measure urinary melatonin levels, providing a non-invasive method to assess melatonin production over the prior 24 hours by using Melatonin sulfate ELISA kit by IBL international hamburg,germany. Blood samples were drawn under aseptic conditions using a 10 mL syringe and analysed for lipid profiles (including triglycerides, HDL, and total cholesterol), fasting and post prandial blood sugar was measured with glucometer and other biochemical parameters relevant to MetS. Anthropometric measurements, including BMI and Waist circumference, were calculated to assess obesity and central fat distribution, while BP was measured with a standard sphygmomanometer after allowing the patient to rest for at least 5 minutes. There were no anticipated serious adverse events (SAEs) during the study, as the data collection procedures were non-invasive, minimising the risk of harm to participants. The primary laboratory investigations included assessments of urine melatonin levels to evaluate circadian rhythm and overall melatonin production, fasting and postprandial blood glucose levels to measure glycaemic status, and a fasting lipid profile to assess cholesterol and triglyceride levels.

Data Processing and Statistical Analysis: Data was entered into Microsoft Excel and was analysed using SPSS version 22.

- **Descriptive Statistics:** This included calculating the mean, standard deviation (SD), median, IQR and correlation coefficients.
- **Inferential Statistics:** Pearson's correlation to analyse the relationship between urinary melatonin levels and individual MetS components. To compare the means of various groups (e.g., between individuals with MetS and those without), the independent t-test was applied with $p < 0.05$ considered significant.

METHODS: Data is analysed using statistical software R version 4.4.2. and Microsoft Excel. Categorical variables given in the form of frequency tables. Continuous variables given in Mean ± SD /Median (Min, Max) form. Chi square test is used to check the association of categorical variables. Normality of variable is checked by Shapiro Wilk test and QQ plot. If data follows normal distribution, parametric tests will be used. Otherwise, non-parametric tests will be used. Two sample t test is used to compare the mean of variables over urine melatonin level at 24 hours. Mann Whitney U test is used to compare the distribution of variables over urine melatonin level at 24 hours. Spearman's rank correlation test is used to check the correlation of different variables with urine melatonin level at 24 hours. P-value less than or equal to 0.05 indicates statistical significance.

RESULTS

The dataset consists of measurements from 120 subjects. The following table gives the distribution of subjects according to demographic details.

Table 1: Distribution of subjects according to demographic details.

Variables	Sub Category	Number of subjects (%)
Age (years)	Mean ± SD Median (Min, Max)	58.23 ± 12.6 58 (29, 86)
Sex	Female	38 (31.67%)
	Male	82 (68.33%)

The mean age of the participants was 58.23 ± 12.6 years, with a median age of 58 years (ranging from 29 to 86 years). In terms of gender distribution, the study included 38 (31.67%) females and 82 (68.33%) males, indicating a higher proportion of male participants.

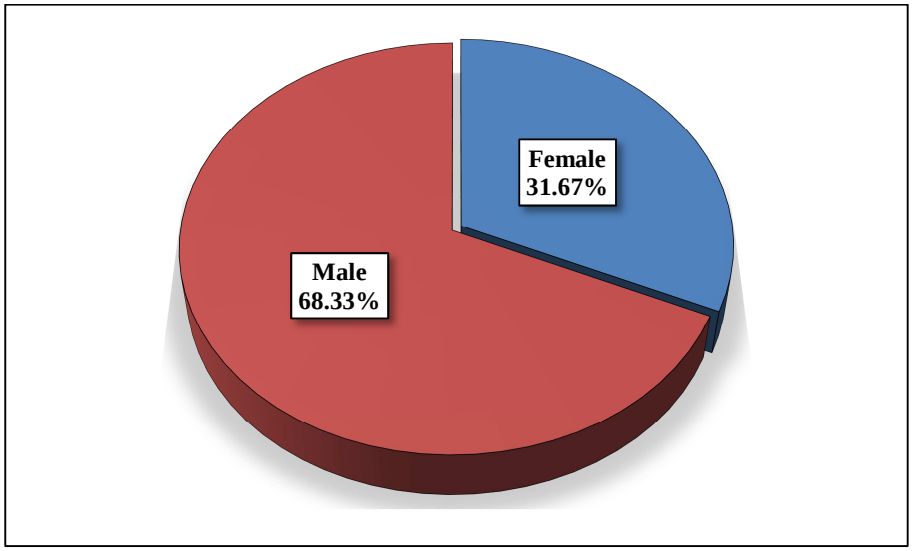

Figure 4: Distribution of subjects according to sex.

The following table gives the distribution of subjects according to Anthropometric Measurements.

Table 2: Distribution of subjects according to Anthropometric Measurements.

Variables	Sub Category	Number of subjects (%)
Weight	Mean ± SD Median (Min, Max)	74.03 ± 12.49 73 (44, 106)
Height	Mean ± SD Median (Min, Max)	163.69 ± 7.5 163.5 (149, 180)
BMI	Normal	20 (16.67%)
	Overweight	11 (9.17%)
	Obesity class 1	53 (44.17%)
	Obesity class 2	36 (30%)
	Mean ± SD Median (Min, Max)	27.52 ± 4.05 27.8 (18.7, 38.3)
Waist Circumference	Healthy	15 (12.5%)
	Unhealthy	105 (87.5%)
	Mean ± SD Median (Min, Max)	95.08 ± 7.56 93 (82, 117)

The mean weight of participants was 74.03 ± 12.49 cm, with a median of 73 cm (ranging from 44 to 106 cm). The mean height was 163.69 ± 7.5 kg, with a median of 163.5 kg (ranging from 149 to 180 kg).

In terms of BMI categories, only 16.67% of subjects had a normal BMI, while 9.17% were overweight. The majority were classified as obese, with 44.17% in obesity class 1 and 30% in obesity class 2. The mean BMI was 27.52 ± 4.05, with a median of 27.8 (ranging from 18.7 to 38.3).

For waist circumference, which is an important indicator of central obesity, 87.5% had an unhealthy waist circumference, while only 12.5% fell within a healthy range. The mean waist circumference was 95.08 ± 7.56 cm, with a median of 93 cm (ranging from 82 to 117 cm).

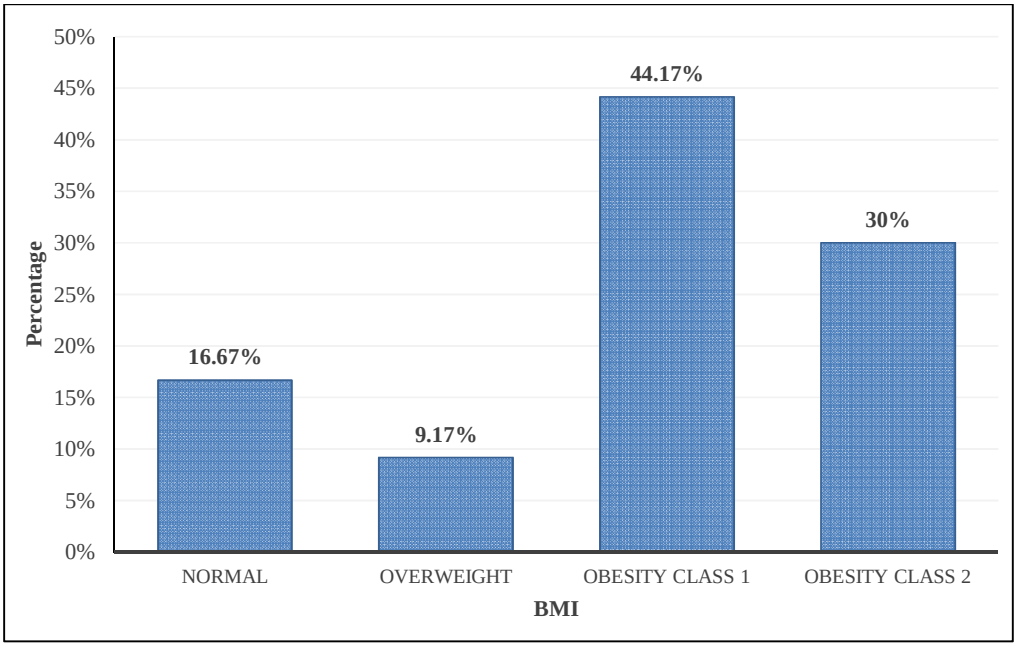

Figure 5: Distribution of subjects according to BMI.

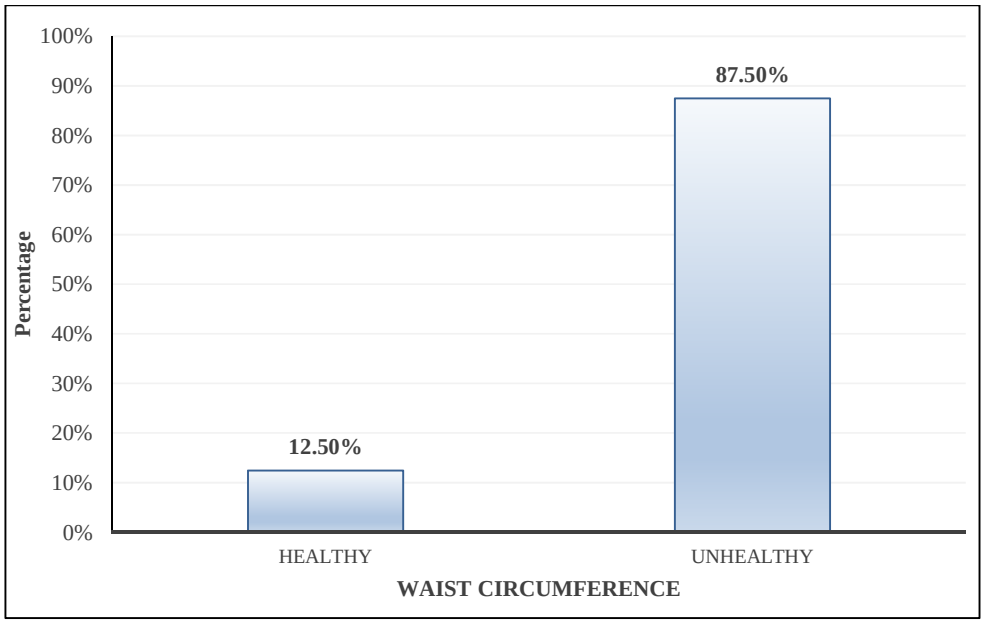

Figure 6: Distribution of subjects according to waist circumference.

The following table gives the distribution of subjects according to Blood Sugar Parameters.

Table 3: Distribution of subjects according to Blood Sugar Parameters.

Variables	Sub Category	Number of subjects (%)
FBS	<100	4 (3.33%)
	≥100	116 (96.67%)
	Mean ± SD Median (Min, Max)	162.04 ± 58.65 142 (88, 332)
PPBS	Mean ± SD Median (Min, Max)	182.29 ± 69.9 156 (102, 430)
HBA1C	Normal	18 (15%)
	Prediabetic	24 (20%)
	Diabetic	78 (65%)
	Mean ± SD Median (Min, Max)	7.88 ± 2.43 7.2 (4.3, 16.7)

Fasting blood sugar (FBS) was ≥100 mg/dL in 96.67% of subjects, with only 3.33% having normal FBS levels (<100 mg/dL). The mean FBS was 162.04 ± 58.65 mg/dL, with a median of 142 mg/dL (ranging from 88 to 332 mg/dL).

For postprandial blood sugar (PPBS), the mean was 182.29 ± 69.9 mg/dL, with a median of 156 mg/dL (ranging from 102 to 430 mg/dL).

Regarding HbA1c levels, 65% of subjects were in the diabetic range, while 20% were prediabetic, and only 15% had normal levels. The mean HbA1c was 7.88 ± 2.43%, with a median of 7.2% (ranging from 4.3 to 16.7%).

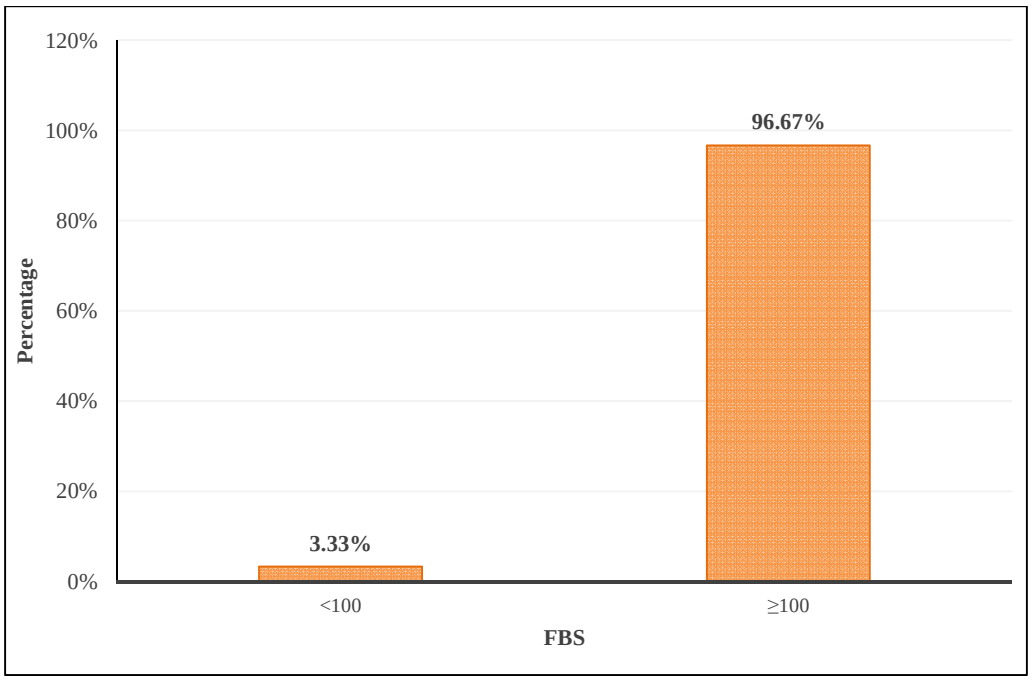

Figure 7: Distribution of subjects according to FBS.

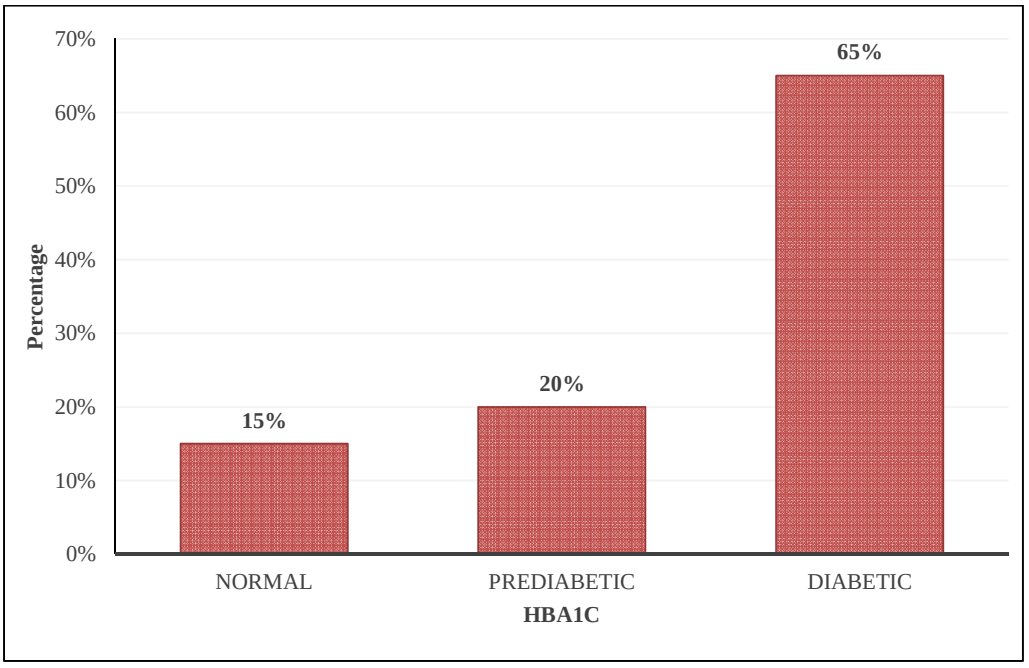

Figure 8: Distribution of subjects according to HBA1C.

The following table gives the distribution of subjects according to blood pressure.

Table 4: Distribution of subjects according to blood pressure.

Variables	Sub Category	Number of subjects (%)
SBP	Mean ± SD Median (Min, Max)	147.47 ± 10.95 146 (120, 180)
DBP	Mean ± SD Median (Min, Max)	91.92 ± 4.78 90 (80, 110)

The mean systolic blood pressure (SBP) was 147.47 ± 10.95 mmHg, with a median of 146 mmHg (ranging from 120 to 180 mmHg). The mean diastolic blood pressure (DBP) was 91.92 ± 4.78 mmHg, with a median of 90 mmHg (ranging from 80 to 110 mmHg).

The following table gives the distribution of subjects according to duration of DM.

Table 5: Distribution of subjects according to duration of DM.

Duration of DM	Number of subjects (%)
No diabetes	18 (15%)
1-5 years	47 (39.17%)
6-10 years	37 (30.83%)
11-15 years	15 (12.5%)
>15 years	3 (2.5%)
Mean ± SD Median (Min, Max)	5.82 ± 4.84 5 (0, 20)

15% of subjects did not have diabetes, while 39.17% had DM for 1-5 years, making this the most common category. 30.83% had DM for 6-10 years, while 12.5% had it for 11-15 years, and only 2.5% had DM for more than 15 years. The mean duration of DM was 5.82 ± 4.84 years, with a median of 5 years (ranging from 0 to 20 years).

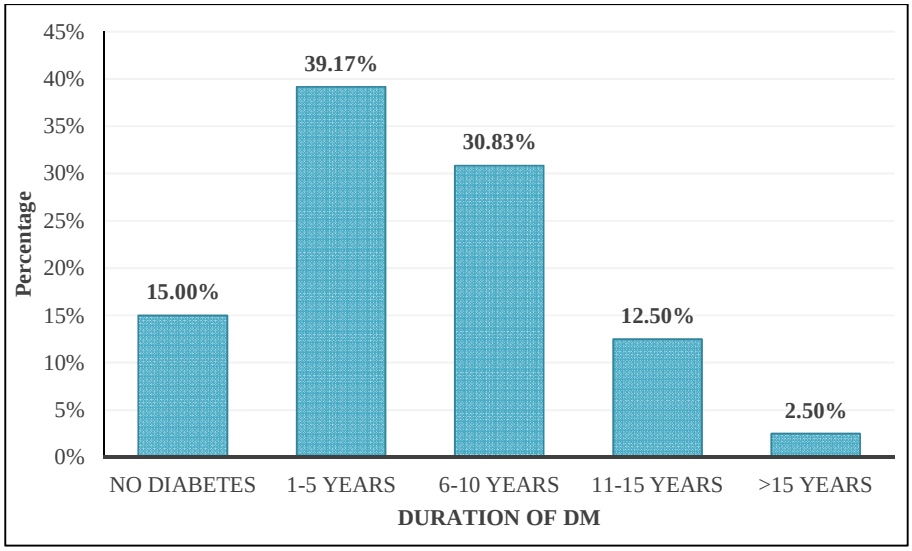

Figure 9: Distribution of subjects according to duration of DM.

The following table gives the distribution of subjects according to comorbidity.

Table 6: Distribution of subjects according to comorbidity.

Variables	Sub Category	Number of subjects (%)
HTN	No	17 (14.17%)
	Yes	103 (85.83%)
IHD	No	96 (80%)
	Yes	24 (20%)
DM	No	18 (15%)
	Yes	102 (85%)

Hypertension (HTN) was the most common condition, affecting 85.83% of subjects, while only 14.17% did not have HTN. Ischemic heart disease (IHD) was present in 20% of subjects, with the majority (80%) being free of the condition. Similarly, diabetes mellitus (DM) was prevalent in 85% of subjects, while 15% did not have DM.

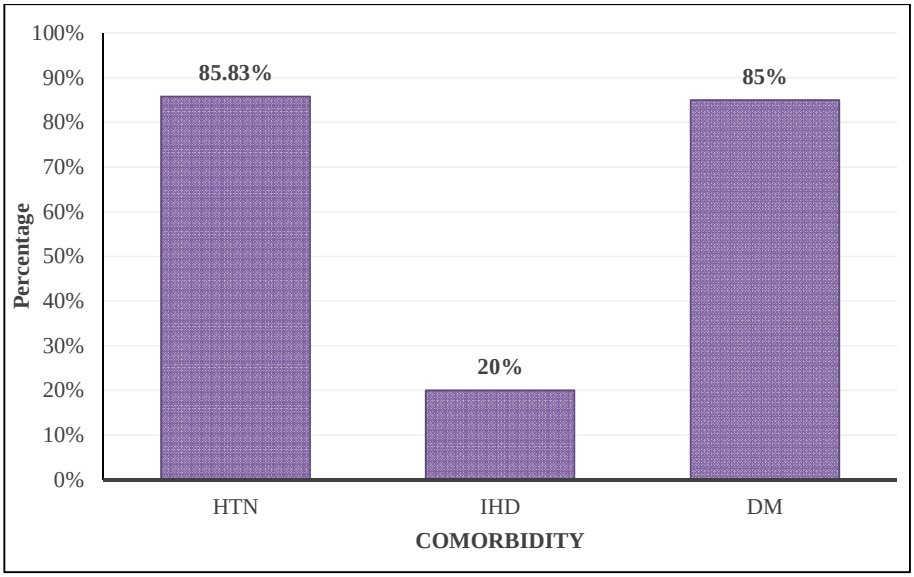

Figure 10: Distribution of subjects according to comorbidity.

The following table gives the distribution of subjects according to Lipid profile.

Table 7: Distribution of subjects according to lipid profile.

Variables	Sub Category	Number of subjects (%)
HDL	<40	86 (71.67%)
	40-60	33 (27.5%)
	>60	1 (0.83%)
	Mean ± SD	31.99 ± 11.72
	Median (Min, Max)	31.5 (10, 71)
TG	Normal	72 (60%)
	Borderline high	20 (16.67%)
	High	27 (22.5%)
	Very high	1 (0.83%)
	Mean ± SD	157.01 ± 92.93
	Median (Min, Max)	132 (11.4, 584)

Total cholesterol	Normal	110 (91.67%)
	Borderline high	8 (6.67%)
	High	2 (1.67%)
	Mean ± SD	135.98 ± 45.69
	Median (Min, Max)	136.5 (39, 259)
LDL	Normal	87 (72.5%)
	Near normal	19 (15.83%)
	Borderline high	12 (10%)
	High	2 (1.67%)
	Mean ± SD	78.77 ± 36.99
	Median (Min, Max)	78 (3, 177)

Low HDL levels were common, with 71.67% of subjects having HDL below 40 mg/dL, while only 0.83% had levels above 60 mg/dL. The mean HDL was 31.99 ± 11.72, with a median of 31.5 mg/dL. Triglyceride (TG) levels were normal in 60% of subjects, but 22.5% had high levels. The mean TG was 157.01 ± 92.93, with a median of 132 mg/dL. Total cholesterol was normal in most subjects (91.67%), with only a small percentage having borderline high or high levels. The mean total cholesterol was 135.98 ± 45.69, with a median of 136.5 mg/dL. LDL levels were also mostly normal (72.5%), while 10% had borderline high levels, and only 1.67% had high levels. The mean LDL was 78.77 ± 36.99, with a median of 78 mg/dL.

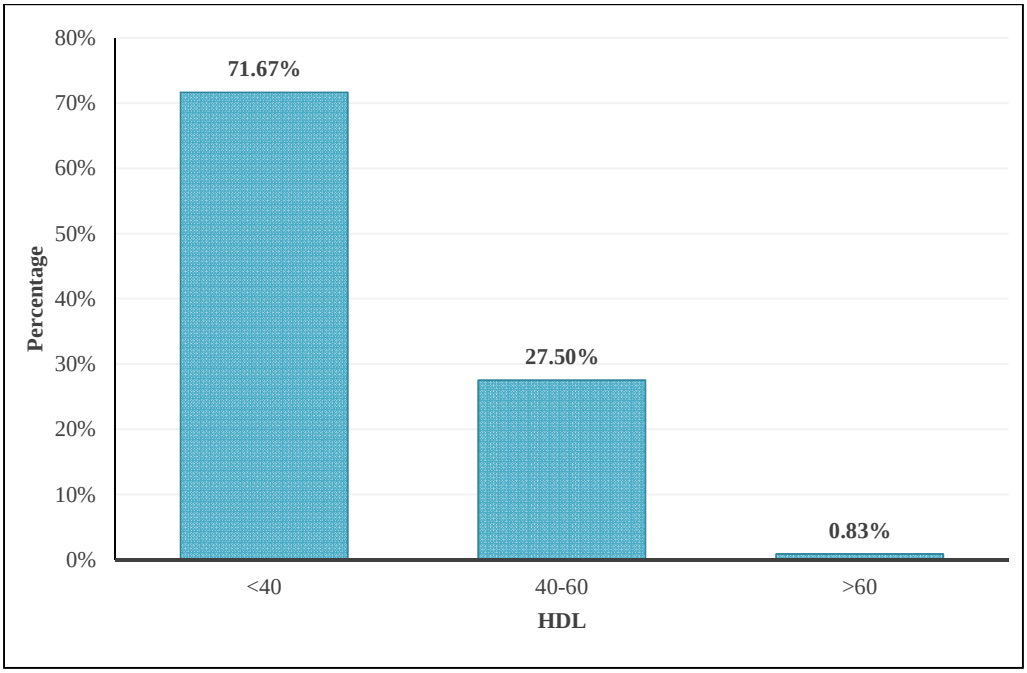

Figure 11: Distribution of subjects according to HDL.

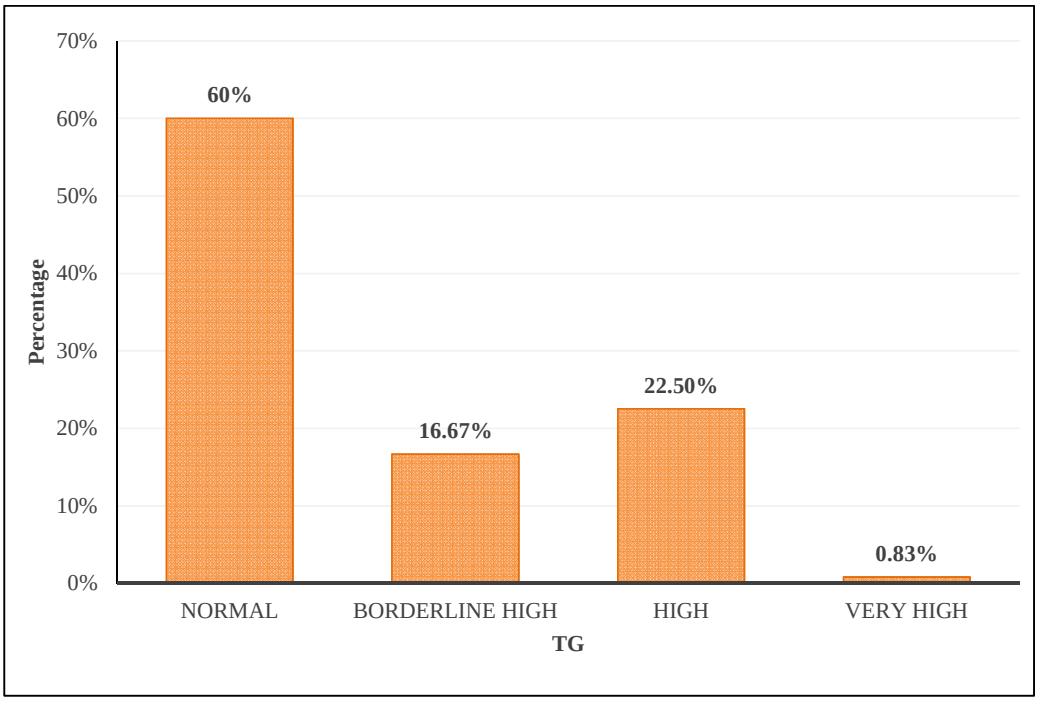

Figure 12: Distribution of subjects according to TG.

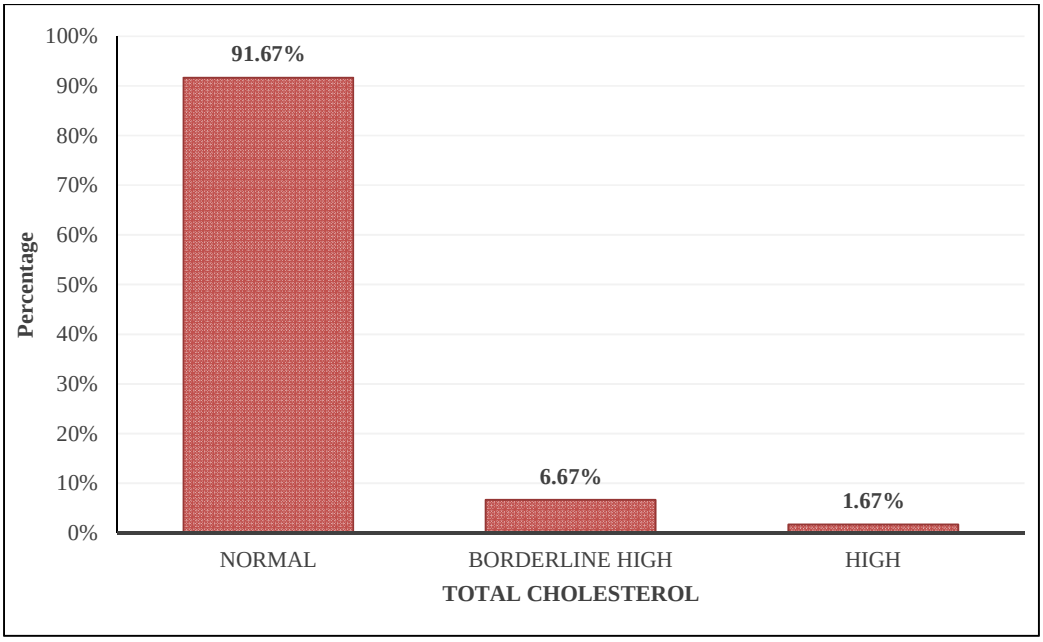

Figure 13: Distribution of subjects according to Total cholesterol.

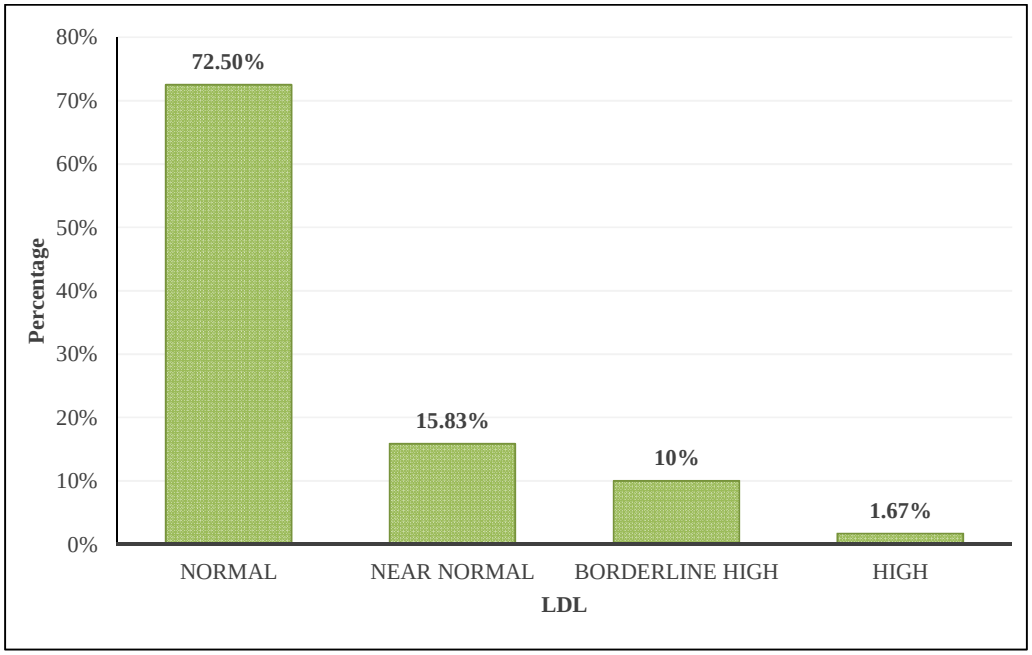

Figure 14: Distribution of subjects according to LDL.

The following table gives the distribution of subjects according to urine melatonin level at 24 hours.

Table 8: Distribution of subjects according to urine melatonin level at 24 hours.

Variables	Sub Category	Number of subjects (%)
Urine melatonin level (ng/ml)	Mean ± SD Median (Min, Max)	10.77 ± 17.2 6.35 (0.26, 134)
Urine melatonin level at 24 hours	Abnormal	49 (40.83%)
	Normal	71 (59.17%)
	Mean ± SD Median (Min, Max)	21.5 ± 34.4 12.7 (0.52, 267.8)

The mean urine melatonin level was 10.77 ± 17.2 ng/ml, with a median of 6.35 (ranging from 0.26 to 134). Urinary melatonin level at 24 hours had a mean value of 21.5 ± 34.4, with a median of 12.7 (ranging from 0.52 to 267.8). Urine melatonin levels at 24 hours were abnormal in 49 (40.83%) subjects and normal in 71 (59.17%) subjects.

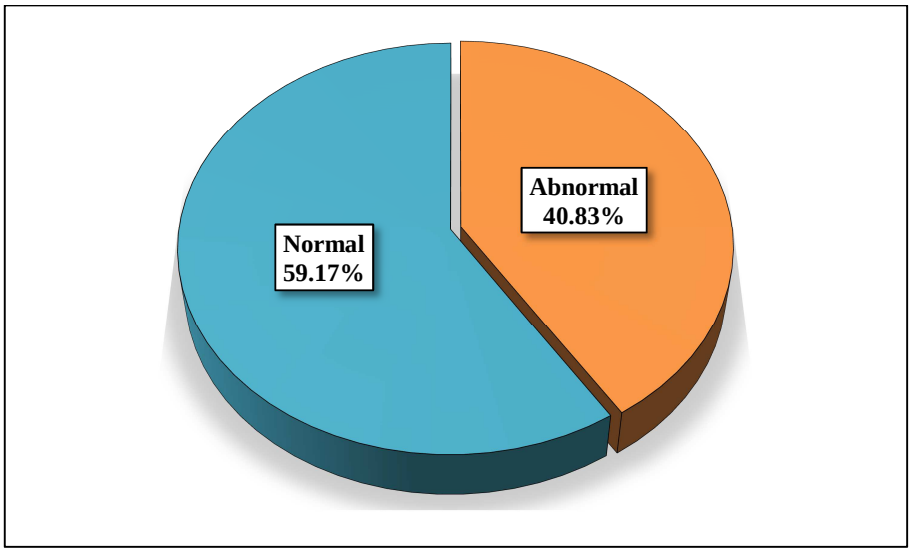

Figure 15: Distribution of subjects according to Urine melatonin level at 24 hours.

The following table gives the comparison of demographic details over urine melatonin level at 24 hours.

Table 9: Comparison of demographic details urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	**Normal**	
Age (years)	Mean ± SD Median (Min, Max)	60.84 ± 12.85 59 (37, 86)	56.44 ± 12.19 58 (29, 80)	0.0597^{t}
Sex	Female	13 (26.53%)	25 (35.21%)	0.3150^{C}
	Male	36 (73.47%)	46 (64.79%)	

Abbreviation: t – Two sample t test, C – Chi square test.

The mean age was slightly higher in the abnormal melatonin group (60.84 ± 12.85 years) compared to the normal melatonin group (56.44 ± 12.19 years), but the difference was not statistically significant (p-value = 0.0597).

In terms of sex distribution, males were more common in both groups, with 73.47% in the abnormal melatonin group and 64.79% in the normal melatonin group, but this difference was also not significant (p-value = 0.3150).

The following table gives the comparison of Anthropometric Measurements over urine melatonin level at 24 hours.

Table 10: Comparison of Anthropometric Measurements over urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	Normal	
Weight	Mean ± SD	73.99 ± 12.82	74.06 ± 12.35	0.3362[MW]
	Median (Min, Max)	76 (54, 106)	73 (44, 99)	
Height	Mean ± SD	162.98 ± 7.55	164.18 ± 7.49	0.9730[t]
	Median (Min, Max)	162 (152, 180)	166 (149, 179)	
BMI	Normal	6 (12.24%)	14 (19.72%)	0.7571[MC]
	Overweight	5 (10.2%)	6 (8.45%)	
	Obesity class 1	23 (46.94%)	30 (42.25%)	
	Obesity class 2	15 (30.61%)	21 (29.58%)	
	Mean ± SD	27.87 ± 4.22	27.28 ± 3.93	0.4420[t]
	Median (Min, Max)	28.4 (18.7, 38.3)	27.6 (19.3, 36.6)	
Waist Circumference	Healthy	9 (18.37%)	6 (8.45%)	0.1064[C]
	Unhealthy	40 (81.63%)	65 (91.55%)	
	Mean ± SD	93.82 ± 7.47	95.96 ± 7.55	0.1151[MW]
	Median (Min, Max)	92 (82, 110)	94 (82, 117)	

Abbreviation: t – Two sample t test, MW – Mann Whitney U test, C – Chi square test, MC – Chi square test with Monte Carlo simulation.

There was no significant relationship between urine melatonin levels at 24 hours and Anthropometric Measurements (p-values > 0.05).

The following table gives the comparison of blood sugar parameters over urine melatonin level at 24 hours.

Table 11: Comparison of blood sugar parameters over urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	Normal	
FBS	<100	1 (2.04%)	3 (4.23%)	0.6562[MC]
	≥100	48 (97.96%)	68 (95.77%)	
	Mean ± SD	162.24 ± 58.62	161.9 ± 59.09	0.8559[MW]
	Median (Min, Max)	142 (92, 332)	142 (88, 308)	
PPBS	Mean ± SD	182.31 ± 64	182.28 ± 74.15	0.7386[MW]
	Median (Min, Max)	166 (107, 367)	154 (102, 430)	
HBA1C	Normal	7 (14.29%)	11 (15.49%)	0.9820[C]
	Prediabetic	10 (20.41%)	14 (19.72%)	
	Diabetic	32 (65.31%)	46 (64.79%)	
	Mean ± SD	7.68 ± 2.29	8.02 ± 2.53	0.5731[MW]
	Median (Min, Max)	7 (4.6, 16.7)	7.3 (4.3, 14.5)	

Abbreviation: MW – Mann Whitney U test, C – Chi square test, MC – Chi square test with Monte Carlo simulation.

There was no significant relationship between urine melatonin levels and blood sugar parameters (p-values > 0.05).

The following table gives the comparison of blood pressure over urine melatonin level at 24 hours.

Table 12: Comparison of blood pressure over urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	Normal	
SBP	Mean ± SD	145.92 ± 9.94	148.54 ± 11.55	0.1347[MW]
	Median (Min, Max)	140 (130, 180)	150 (120, 180)	
DBP	Mean ± SD	91.27 ± 4.01	92.37 ± 5.22	0.2035[MW]
	Median (Min, Max)	90 (86, 110)	90 (80, 110)	

Abbreviation: MW – Mann Whitney U test.

There was no significant relationship between urine melatonin levels at 24 hours and blood pressure parameters (p-values > 0.05).

The following table gives the comparison of lipid profile over urine melatonin level at 24 hours.

Table 13: Comparison of lipid profile over urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	Normal	
HDL	<40	36 (73.47%)	50 (70.42%)	0.4668[MC]
	40-60	12 (24.49%)	21 (29.58%)	
	>60	1 (2.04%)	(0%)	
	Mean ± SD Median (Min, Max)	32.16 ± 13.07 30 (10, 71)	31.87 ± 10.78 33 (10, 53)	0.8946[t]
TG	Normal	31 (63.27%)	41 (57.75%)	0.7771[MC]
	Borderline high	9 (18.37%)	11 (15.49%)	
	High	9 (18.37%)	18 (25.35%)	
	Very high	(0%)	1 (1.41%)	
	Mean ± SD Median (Min, Max)	138.54 ± 75.47 129 (11.4, 457)	169.77 ± 101.84 140 (11.4, 584)	0.1222[MW]
Total cholesterol	Normal	46 (93.88%)	64 (90.14%)	0.0608[MC]
	Borderline high	1 (2.04%)	7 (9.86%)	
	High	2 (4.08%)	(0%)	
	Mean ± SD Median (Min, Max)	129.06 ± 48.11 129 (50, 259)	140.76 ± 43.64 145 (39, 220)	0.1689[t]
LDL	Normal	38 (77.55%)	49 (69.01%)	0.6952[MC]
	Near normal	7 (14.29%)	12 (16.9%)	
	Borderline high	3 (6.12%)	9 (12.68%)	
	High	1 (2.04%)	1 (1.41%)	
	Mean ± SD Median (Min, Max)	73.65 ± 38.35 74 (3, 177)	82.3 ± 35.87 78 (11, 162)	0.2098[t]

Abbreviation: t – Two sample t test, MW – Mann Whitney U test, MC – Chi square test with Monte Carlo simulation.

There was no significant relationship between urine melatonin levels at 24 hours and any lipid profile parameter (p-values > 0.05).

The following table gives the comparison of comorbidity over urine melatonin level at 24 hours.

Table 14: Comparison of comorbidity over urine melatonin level at 24 hours.

Variables	Sub Category	Urine melatonin level at 24 hours		p-value
		Abnormal	Normal	
HTN	No	3 (6.12%)	14 (19.72%)	**0.0358[C]***
	Yes	46 (93.88%)	57 (80.28%)	
IHD	No	40 (81.63%)	56 (78.87%)	0.7103[C]
	Yes	9 (18.37%)	15 (21.13%)	
DM	No	4 (8.16%)	14 (19.72%)	0.0814[C]
	Yes	45 (91.84%)	57 (80.28%)	

*Abbreviation: C – Chi square test, * indicates statistical significance.*

Hypertension (HTN) was significantly more common in the abnormal melatonin group (93.88%) compared to the normal melatonin group (80.28%), with a p-value of 0.0358.

Ischemic heart disease (IHD) and diabetes (DM) were similarly distributed between both groups, with no significant difference (p-values > 0.05).

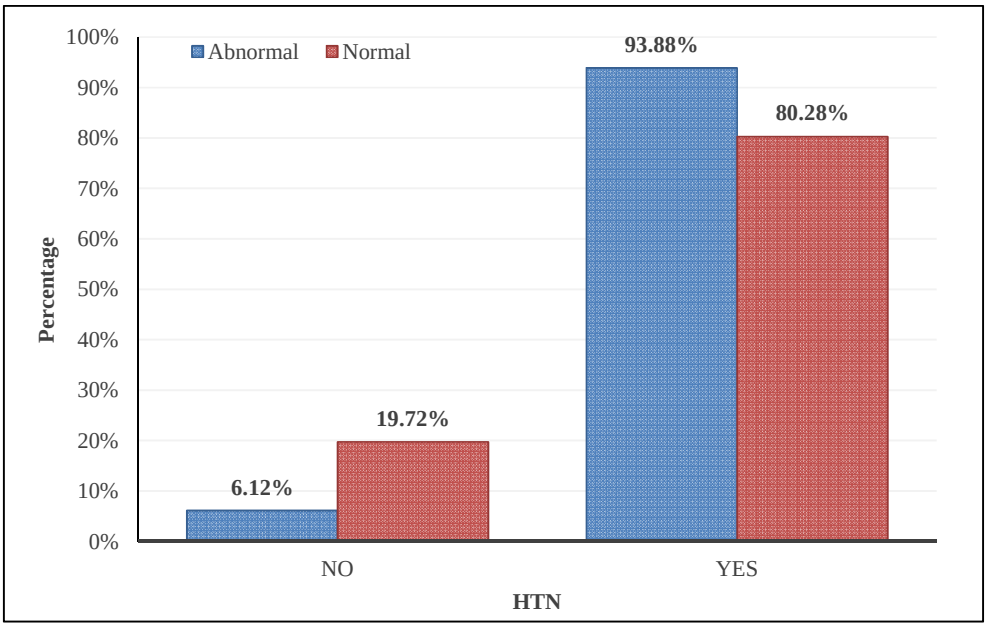

Figure 16: Distribution of HTN over Urine melatonin level.

The following table gives the comparison of duration of DM over urine melatonin level at 24 hours.

Table 15: Comparison of duration of DM over urine melatonin level at 24 hours.

Duration of DM	Urine melatonin level at 24 hours		p-value
	Abnormal	Normal	
No diabetes	4 (8.16%)	14 (19.72%)	0.3718^{MC}
1-5 years	22 (44.9%)	25 (35.21%)	
6-10 years	14 (28.57%)	23 (32.39%)	
11-15 years	7 (14.29%)	8 (11.27%)	
>15 years	2 (4.08%)	1 (1.41%)	
Mean ± SD	6.45 ± 5.03	5.38 ± 4.68	0.2433^{MW}
Median (Min, Max)	5 (0, 20)	5 (0, 20)	

Abbreviation: MW – Mann Whitney U test, MC – Chi square test with Monte Carlo simulation.

The distribution of diabetes duration was similar between both groups (p-value = 0.3718). The mean duration of diabetes was 6.45 ± 5.03 years in the abnormal melatonin group and 5.38 ± 4.68 years in the normal melatonin group, with no significant difference (p-value = 2433).

The following table gives the correlation of urine melatonin level at 24 hours with different variables.

Table 16: Correlation of urine melatonin level at 24 hours with different variables.

Variables	Correlation coefficient	p-value [SP]
Age	-0.1395	0.1286
Weight	-0.0130	0.8877
Height	0.0907	0.3244
BMI	-0.0706	0.4436
Waist Circumference	0.1074	0.2427
FBS	0.0024	0.9794
PPBS	0.0026	0.9777
SBP	0.0045	0.9611
DBP	0.0880	0.3391
HDL	-0.0264	0.7749
TG	-0.0018	0.9846
Total cholesterol	0.0547	0.5532
LDL	-0.0196	0.8314
HBA1C	0.0954	0.2998
Duration of DM	-0.0700	0.4471

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

Most of the variables, including age, weight, height, BMI, waist circumference, blood sugar levels (FBS, PPBS, HBA1C), blood pressure (SBP, DBP), lipid profile (HDL, TG, total cholesterol, LDL), and diabetes duration, showed no significant correlation with urine melatonin levels at 24 hours (p-values > 0.05).

DISCUSSION

In this study, the mean age of the participants was 58.23 ± 12.6 years, ranging from 29 to 86 years. The study included 31.67% females and 68.33% males indicating a higher proportion of male participants. This corresponds with the literature that MetS has been seen in as low as 18 years as well, and its prevalence increases with age. However, contrary to our findings, recent literature suggests that prevalence is consistently significantly higher among women than men in India.[7,85]

The majority of the study population (74.17%) fell into obesity classes 1 and 2, which is consistent with the strong association between obesity and MetS. These findings are in line with a study by Mata et al., which reported a higher prevalence of MetS among pre-obese (56.9%) and obese (62.4%). It also highlighted a significant burden of MetS, even in individuals with normal BMI.[86] Similarly, Meigs reported that among 638 obese individuals, 63% had MetS.[87] Obesity, particularly visceral adiposity, is a key driver of insulin resistance, inflammation, and dyslipidemia, all of which are central to the pathophysiology of MetS.[61]

For waist circumference, in this study, 87.5% of participants had an unhealthy waist circumf.erence. Studies have reported that waist circumference is a stronger predictor of metabolic risk than overall obesity, as visceral fat is more metabolically active and contributes to insulin resistance, dyslipidemia, and hypertension.[88]

Blood Sugar, Blood pressure, Comorbidity and Lipid profile

In this study, FBS was ≥100 mg/dL in 96.67% of subjects, mean FBS was 162.04 ± 58.65 mg/dL. For postprandial blood sugar (PPBS), the mean was 182.29 ± 69.9 mg/dL. Regarding HbA1c levels, 65% of subjects were in the diabetic range, 20% were prediabetic, and 15% had normal levels. Among the study participants,

39.17% had DM for 1-5 years, followed by 30.83% who had DM for 6-10 years. The findings highlight a strong association between MetS and diabetes, which is consistent with existing literature. A review reported a pooled prevalence of MetS of 64.49% among individuals with type 2 diabetes mellitus (T2DM).[89] Another study found the prevalence of MetS to be 60.62% among T2DM patients.[90] Another study reported an even higher prevalence, with 87.5% of T2DM patients having MetS.[91]

In this study, the mean SBP was 147.47 ± 10.95 mmHg (range: 120–180 mmHg), and the mean DBP was 91.92 ± 4.78 mmHg (range: 80–110 mmHg). The mean SBP falls within the Stage 2 hypertension category (SBP ≥140 mmHg) according to the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, indicating that most participants had poorly controlled hypertension. The mean DBP falls within the Stage 1 hypertension category (DBP ≥80 mmHg), reflecting a high prevalence of hypertension in this population. Hypertension is a key component of MetS and a major risk factor for CVD and stroke. These findings are consistent with studies reporting a high prevalence of hypertension in MetS patients. Basu et al. reported hypertension as the most prevalent component of MetS, affecting 98.55% of individuals.[92] Thakur et al. found that MetS was present in 68.6% of hypertensive patients based on modified NCEP-ATP III criteria and 63.6% based on IDF criteria.[93] Pemminati et al. reported an overall hypertension prevalence of 65.8% in individuals with MetS.[94] These findings highlight the strong association between MetS and hypertension.

In this study, HTN was the most common condition, affecting 85.83% of subjects, while 14.17% did not have HTN. Similarly, DM was prevalent in 85% of subjects, while 15% did not have DM. This is in line with a study by Basu et al., hypertension was the most prevalent component of metabolic syndrome (98.55%),

followed by abdominal obesity (94.57%), diabetes mellitus (89.40%), and hypercholesterolemia (25.47%).[92]

We found that Low HDL levels were common, with 71.67% of subjects having HDL below 40 mg/dL. While 60% of participants had normal TG levels (<150 mg/dL), the mean TG level was slightly above the normal range. Total cholesterol was normal in most subjects (91.67%), and LDL levels were also mostly normal (72.5%). The high prevalence of low HDL cholesterol is consistent with the dyslipidaemia pattern seen in MetS. It is often driven by insulin resistance, obesity, and elevated triglyceride levels. HDL cholesterol plays a protective role in cardiovascular health by promoting reverse cholesterol transport and reducing inflammation. Low HDL levels significantly increase the risk of atherosclerosis and CVD.[95,96] A study by Mani et al. found that low HDL-P is independently linked to the development of metabolic syndrome (MetS) after accounting for traditional risk factors, lipid levels, adiposity, inflammation, and insulin resistance markers.[97]

Urine melatonin level at 24 hours

In this study, the mean urine melatonin level was 10.77 ± 17.2 ng/mL, ranging from 0.26 to 134 ng/mL. The mean urinary melatonin level in this study population was relatively low, with a wide variability. Lower melatonin levels have been associated with metabolic disturbances, including insulin resistance, obesity, and hypertension.[18,80] Some individuals had very low levels (e.g., 0.26 ng/mL), while others had relatively high levels (e.g., 134 ng/mL). This variability may reflect differences in circadian rhythm regulation, sleep quality, or underlying metabolic abnormalities.

In this study, urinary melatonin levels at 24 hours were abnormal in 40.83% and normal in 59.17%, which may indicate that melatonin dysregulation is not universal in MetS. Abnormal melatonin levels may contribute to disrupted sleep patterns, impaired glucose metabolism, and increased oxidative stress, all of which are relevant to MetS.[18] These studies have reported altered melatonin levels in individuals with metabolic disorders. The study by Balliuzek et al. highlighted that the correlation between melatonin hypersecretion and MetS symptoms depends on the patient's age. Melatonin levels could thus be used as a biological marker and prognostic factor for the progression of MetS.[75] However, a study showed no changes in melatonin concentrations between the two groups, indicating that melatonin secretion remained unimpaired in MetS patients.[77] A study by Mahmood and Hilal showed significantly lower melatonin levels in MetS patients (206.55 ± 105 pg/ml) compared to controls (298.82 ± 110.4 pg/ml).[80]

Comparison of Demographic, Clinical Characteristics and Urine Melatonin Levels

In this study, the mean age was slightly higher in the abnormal melatonin group (60.84 ± 12.85 years) compared to the normal melatonin group (56.44 ± 12.19 years), but the difference was not statistically significant (p-value = 0.0597). Males were more common in both groups, with 73.47% in the abnormal melatonin group and 64.79% in the normal melatonin group, but this difference was also not significant (p-value = 0.3150). Urine melatonin levels at 24 hours showed no significant relationship with anthropometric measurements, blood sugar parameters, blood pressure, or lipid profile. The lack of a significant relationship suggests that melatonin dysregulation may not directly influence these metabolic parameters in MetS patients.

Hypertension was significantly more common in the abnormal melatonin group (93.88%) compared to the normal melatonin group (80.28%) ($p = 0.0358$). However, no significant differences were observed in the distribution of IHD, DM, or diabetes duration between the two groups (p-values > 0.05). The significant association between abnormal melatonin levels and hypertension highlights the potential role of melatonin in blood pressure regulation. This aligns with the literature.[98,99]

Correlation of Urine Melatonin Levels with Variables

In this study, the correlation coefficients for all variables are close to zero, ranging from -0.1395 to 0.1074, indicating weak or negligible relationships between urinary melatonin levels and the measured variables. Most variables, including age, weight, height, BMI, waist circumference, blood sugar levels (FBS, PPBS, HbA1c), blood pressure (SBP, DBP), lipid profile (HDL, TG, total cholesterol, LDL), and diabetes duration, showed no significant correlation with urine melatonin levels at 24 hours (p-values > 0.05). A multinational study reported that mean melatonin concentration was found to negatively correlate with age, weight, and height.[100] A study reported that lower melatonin secretion was independently associated with a higher risk of developing type 2 diabetes.[101] Similarly, another study reported that melatonin levels are independently and inversely associated with incident hypertension.[102]

The lack of significant correlations in our study suggests that melatonin dysregulation in MetS patients may be influenced by factors not captured here, such as circadian rhythm disruption, sleep quality, or oxidative stress. Melatonin levels may act as an independent marker of metabolic health rather than being directly linked to specific anthropometric or metabolic parameters. Although the correlation

analysis did not show a significant relationship between melatonin levels and blood pressure, the earlier finding of a higher prevalence of hypertension in the abnormal melatonin group suggests a potential indirect link, possibly mediated by mechanisms such as endothelial function or oxidative stress. Future research should explore the complex interplay between melatonin, circadian rhythms, and metabolic health, using longitudinal designs and additional biomarkers to better understand its role in the pathophysiology of MetS.

STRENGTHS

1. The use of standardized diagnostic criteria, NCEP ATP III criteria for diagnosing Metabolic Syndrome (MetS) ensures comparability with other studies.

2. The study employs urinary melatonin levels as a non-invasive biomarker, reducing patient discomfort while providing valuable insights into melatonin metabolism.

3. Inclusion of multiple metabolic parameters (blood glucose, lipid profile, BMI, WHR, and blood pressure) allows for a holistic analysis of MetS and its potential association with melatonin levels.

4. The universal sampling technique ensures that all eligible patients diagnosed with MetS during the study period were included, reducing potential selection bias.

LIMITATIONS

1. Cross-Sectional Design limits the ability to establish causal relationships between urine melatonin levels and other variables.
2. Other unmeasured factors (e.g., sleep patterns, dietary habits, or physical activity) may influence melatonin metabolism and metabolic parameters.
3. Melatonin levels were measured only once (at 24 hours), which may not reflect long-term melatonin patterns. Repeated measurements over time could provide a more accurate assessment of melatonin status.
4. The Melatonin – sulfate ELISA kit does not provide specific range for our study population.
5. Although urine melatonin typically decreases with age ,our study shows significant variation in melatonin levels regardless of age

CONCLUSION

This study reveals a high prevalence of metabolic disorders among participants, with 83.33% being overweight or obese, 85.83% having hypertension, 71.67% exhibiting HDL <40, and 85% diagnosed with diabetes. Additionally, 41.8% of participants had abnormal urine melatonin levels, indicating possible disruptions in melatonin metabolism. The study found that abnormal urine melatonin levels at 24 hours were significantly associated with hypertension but not with other demographic, anthropometric, blood sugar, lipid profile, or comorbidity parameters. The lack of significant correlations between urine melatonin levels and other variables suggests that melatonin levels may not be strongly influenced by these factors in this population. However, the association with hypertension needs further investigation to understand the underlying mechanisms and potential implications for cardiovascular health.

SUMMARY

1. **Demographic and Anthropometric Factors:**
    - The mean age of participants was 58.23 ± 12.6 years, with a higher proportion of males (68.33%).
    - Most participants were obese, with 74.17% falling into obesity classes 1 and 2.
    - Unhealthy waist circumference was observed in 87.5% of subjects, indicating a high prevalence of central obesity.
2. **Blood Sugar Parameters:**
    - The majority of participants had elevated fasting blood sugar (FBS ≥100 mg/dL in 96.67%) and HbA1c levels (65% diabetic, 20% prediabetic).
3. **Blood Pressure, lipid profile and DM:**
    - Hypertension (HTN) was prevalent in 85.83% of subjects, and it was significantly more common in the abnormal melatonin group (93.88%) compared to the normal melatonin group (80.28%) ($p = 0.0358$).
    - No significant differences were found in lipid profile parameters (HDL, TG, total cholesterol, LDL) between the two melatonin groups (p-values > 0.05).
    - The duration of diabetes, the presence of IHD and DM showed no significant differences between the two melatonin groups (p-values > 0.05).
4. Urine melatonin levels at 24 hours showed no significant correlation with age, weight, height, BMI, waist circumference, blood sugar levels, blood pressure, lipid profile, or diabetes duration (p-values > 0.05).

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ANNEXURE – I - INFORMED CONSENT FORM

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Introduction:

The study is aimed at identifying the patients with metabolic syndrome and subjecting them to investigations and clinical examination in whom we will be evaluating the role of melatonin as a possible risk factor in development of metabolic syndrome.

Explanation of procedure:

- The patient will be explained about the procedure in the best possible language they understand.
- Urine sample will be collected at morning 1st urine mid stream sampel or melatonin levels
- The blood will be drawn using 10 ml syringe using all aseptic precaution and it bill be evaluated for BSL and lipid profile.
- BMI, Waist hip ratio will be evaluated.
- Using above data patient will be diagnosed as a metabolic syndrome, and further correlation with melatonin levels will be established using statistical analysis.

Withdrawal from participation in the study:

- The right to participate and withdrawal from the study group is a prerogative of the patient.
- Patient can exercise his/her right to withdrawal from the study with proper intimation to the principal investigation

Possible benefits from participating in the study:

- As such the study is safe and patient who is diagnosed with metabolic syndrome along with deranged melatonin levels if found, will be advised to follow up to medicine OPD regarding diet and lifestyle modification and medical treatment if required.
- So basically it's a win-win situation for participant.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations done during the course of study will be paid by **the principal investigator .**

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups.

However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: **"Name of student/PI, mobile number, email ID"** If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

TO STUDY THE CORRELATION OF URINE MELATONIN WITH METABOLIC SYNDROME AND ITS MANIFESTATION AT TERTIARY CARE HOSPITAL- A CROSS SECTIONAL STUDY

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me inthe language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE – II – DATA COLLECTION FORMAT

- Demographic Details Date:

1. Name of the patient :
2. IP Number:
3. Age:
4. Sex:
5. Address:
6. Occupation:
7. Phone Number:

Chief Complaints:	
Past History	
Personal History	
Treatment History	

- Vitals:

Temperature	
Pulse	
Blood Pressure	
Respiratory Rate	

- Physical Examination:

Index	Yes	No
Pallor		
Icterus		
Cyanosis		
Clubbing		
Lymphadenopathy		
Edema		

- Systemic Examination:

CVS	
RS	
P/A	
CNS	

8. Any History of Ischemic Heart Disease:
9. Any History of Stroke:
10. Risk Factors:

Smoking	Alcohol	Hypertension
Thyroid Disease	Stroke	Cardiovascular Disease
High Cholesterol/Triglycerides		
Diabetes	Others:	

- Investigation and Anthropometrey

• URINE MELATONIN AT 6 AM	•
• HDL	•
• LDL	•
• CHOLESTEROL	•
• TG	•
• HBA1C	•
• FBS	•
• BMI	•
• HIEGHT	•
• WEIGHT	•
• WAIST CIRCUMFERENCE	•

- DIAGNOSTIC CRITERIA FOR METABOLIC SYNDROME

METABOLIC SYNDROME CRITERIA	
HYPERTENTION	
HDL	
TG	
FASTING BLOOD SUGAR	
WAIST CIRCUMFERENCE	

ANNEXURE – III

MASTER CHART

SR NO	IP	AGE	SEX	WEIGHT	HEIGHT	BMI	WAIST CIR	FBS	PPBS	SBP	DBP	HDL	TG	T.CHOL	LDL	HBA1C	DM	HTN	IHD	UMEL ng/ml	MG/24 HR
1	10076460	48	M	65	170	22.5	93	117	165	140	88	39	134	162	78	4.3	0	YES	YES	8.9335	17.86
2	10061760	58	M	98	170	33.9	108	98	103	130	90	36	123	154	102	4.8	4	YES		4.582	9.16
3	10071725	40	M	90	168	29.9	103	104	137	130	90	25	129	119	66	4.9	0	YES	YES	8.527	17.054
4	10074592	44	M	70.2	164	26.1	104	104	134	142	90	15	134	255	74	4.9	2	YES		32.155	64.31
5	10072722	72	M	80	163	30.1	110	92	107	150	90	33	62	62	24	5.1	2	YES		3.7465	7.48
6	10075716	52	M	76	158	30.4	98	128	129	140	90	34	153	196	143	5.2	0	YES	YES	2.2285	4.45
7	10080362	58	F	58	154	24.4	92	119	123	150	90	43	89	154	91	5.4	2	YES		4.099	8.18
8	10076907	59	M	69.5	160	27	98	112	108	150	90	49	67	132	82	5.5	0	YES		2.9365	5.86
9	10076668	45	M	86	173	28.7	104	103	112	140	90	32	205	137	93	5.6	0	NO		3.281	6.56
10	10077656	73	M	73	158	29.2	92	123	134	140	90	20	105	84	34	5.7	4	YES	YES	1.04	2.08
11	10080116	54	M	56	160	21.9	89	122	138	140	90	39	451	186	109	5.7	3	YES		4.08	8.16
12	10078537	72	M	106	180	32.7	110	116	140	160	90	71	99	173	92	5.7	6	YES		3.3685	6.72
13	10081276	56	M	88	172	29	92	117	123	180	90	23	239	153	58	5.7	0	YES		4.242	8.48
14	10072650	39	M	70	162	26.7	89	119	127	138	90	34	66	184	136	5.8	0	NO		12.0535	24.1
15	10074226	62	M	86	173	28.7	92	113	124	140	90	18	121	120	84	5.8	4	YES		4.7065	9.4
16	10075980	31	M	67	173	22.4	92	120	145	140	90	26	105	98	59	6	0	NO		14.3685	28.72
17	10061830	51	M	96	167	34.4	102	121	167	160	90	48	142	217	150	6	5	YES		2.2935	2.58
18	10083125	75	M	90	172	30.2	105	100	108	160	90	43	96	91	30	6	0	YES	YES	4.8835	9.76
19	10076146	57	M	59	170	20.4	97	114	130	160	90	26	88	101	63	6	0	YES		133.998	267.8
20	10078296	35	M	99	175	32.3	108	103	110	160	90	31	193	189	141	6	0	YES		8.1534	16.3
21	10083607	54	M	78	176	25.2	92	114	126	150	90	30	72	130	82	6.1	6	YES		3.115	6.23
22	10077633	45	M	80	178	25.2	96	123	156	140	90	42	160	198	141	6.2	3	YES		2.6275	5.24
23	10075959	44	F	60	154	25.3	94	115	119	140	90	42	104	117	69	6.2	5	YES		2.567	5.134
24	10078930	61	M	72	168	25.5	98	112	102	138	90	39	70	86	40	6.3	6	NO	YES	20.1815	40.36
25	10070649	63	M	72	158	28.8	82	112	118	150	90	18	188	161	89	6.4	2	YES		0.542	1.084
26	10059555	38	M	87	172	29.4	90	120	145	140	90	10	190	93	20	6.4	2	YES		2.5615	5.12
27	10083556	43	F	82	172	27.7	96	128	138	150	90	40	251	196	117	6.4	0	YES		6.5575	13.1

28	10076905	52	M	76	169	26.6	92	112	129	150	90	47	111	130	74	6.4	13	YES		24.3245	48.6
29	10072126	70	M	82	162	31.2	94	142	150	140	90	27	106	91	53	6.6	15	YES	YES	11.6745	23.2
30	10081543	58	F	78	158	31.2	86	123	128	140	90	29	59	98	59	6.6	7	YES		57.251	114.5
31	10077680	65	M	56	170	19.4	82	112	116	136	90	13	226	78	10	6.7	12	YES		0.342	0.68
32	10076475	34	M	82	172	27.7	94	128	132	140	90	37	188	116	58	6.7	3	YES		9.861	19.72
33	10076997	64	M	82	170	28.4	89	200	289	170	100	36	135	154	100	6.7	8	YES		0.297	0.594
34	10076338	70	M	87	170	30.1	102	146	166	140	96	25	118	93	52	6.8	13	NO		106.94	213.8
35	10079022	53	F	54.8	158	22	83	137	147	140	90	27	292	152	87	6.8	2	NO		10.598	21
36	10076071	46	F	63	158	25.2	108	121	145	150	90	36	144	166	114	6.9	8	YES		13.131	26.6
37	10051284	42	M	76	154	32	88	162	189	160	100	40	72	157	110	6.9	2	YES		1.272	2.54
38	10080640	60	M	86	168	30.5	90	120	156	140	90	25	111	152	106	7	5	YES		4.091	8.18
39	10080376	79	F	60	154	25.3	104	115	165	140	90	51	97	93	39	7	8	YES		3.575	7.15
40	10077389	54	M	52.4	149	23.4	94	132	140	160	90	44	163	170	100	7.1	1	YES		4.072	8.14
41	10080104	76	M	56.8	168	20.1	96	132	137	134	90	32	49	91	54	7.2	2	YES	YES	42.306	84.6
42	10083117	58	M	92	170	31	94	134	178	140	90	27	146	178	109	7.2	5	YES		3.0225	6.04
43	10075588	66	F	75	154	31.6	108	112	126	150	100	24	157	136	78	7.2	7	YES		12.667	25.32
44	10062191	58	F	82	158	32.8	90	178	200	150	100	41	147	145	88	7.3	2	YES	YES	4.8265	9.64
45	10081142	78	M	66	179	20.6	94	150	167	170	90	16	63	62	33	7.3	12	YES	YES	6.769	13.5
46	10081372	52	F	59.2	166	21.5	83	207	233	150	100	25	144	121	79	7.4	7	YES		15.993	31.8
47	10072209	86	M	78	172	26.4	84	218	114	150	90	21	95	98	55	7.4	20	YES	YES	0.8965	1.78
48	10080413	72	F	60	154	25.3	96	163	234	140	90	50	175	168	110	7.6	15	YES	YES	2.49	4.98
49	10080005	59	F	54.3	158	22.4	86	186	236	140	90	22	240	120	63	7.6	8	YES		0.26	0.52
50	10077497	70	M	70	166	25.4	95	132	134	140	90	29	66	72	36	7.6	10	YES	YES	1.7745	3.54
51	10060095	55	M	88	172	29.7	92	180	196	160	90	36	140	127	67	7.7	4	YES		7.071	14.14
52	10076755	75	M	77	157	31.2	93	200	234	150	90	58	108	259	177	7.8	10	YES		2.52	5.04
53	10076443	56	F	57	153	24.3	92	123	120	150	100	32	217	191	133	7.9	6	YES		19.055	38.11
54	10079899	70	F	68	152	29.4	99	282	304	150	100	48	130	162	90	8.1	6	YES	YES	6.8105	13.62
55	10081265	56	F	56.8	160	23.4	96	240	278	140	90	30	164	169	110	8.2	8	YES	YES	3.2665	6.52
56	10059891	78	M	104	168	36.8	110	160	231	160	90	30	231	129	75	8.4	10	YES		1.545	3.09
57	10080917	49	M	58	154	24.5	89	178	291	138	90	12	146	50	15	8.7	8	YES		1.544	3.088
58	10064753	84	M	80	164	29.7	90	176	220	140	90	33	110	158	111	8.8	15	YES		1.2485	2.48
59	10077527	42	F	73	168	25.9	92	182	190	140	90	27	128	182	126	9	7	YES		11.825	23.6

60	10065251	60	M	78	158	31.2	90	147	156	150	90	27	255	136	72	9	1	YES	YES	7.113	14.22
61	10074550	66	M	78	168	27.6	92	142	178	140	90	37	125	148	94	9.2	6	YES		0.84	1.68
62	10069041	39	M	86	160	33.6	98	170	199	160	90	28	106	103	60	9.2	4	YES		4.222	8.44
63	10069950	74	M	84	158	31.1	102	126	118	140	90	42	114	42	94	9.3	15	NO		12.735	25.46
64	10080392	52	M	78	154	32.9	90	192	200	140	90	22	203	125	79	9.3	3	YES		29.691	59.38
65	10069835	71	M	70	152	30.3	92	276	256	140	90	26	84	71	34	9.6	8	YES	YES	0.6165	1.232
66	10078060	65	M	98	160	38.3	104	147	157	140	90	60	93	60	26	9.6	15	YES	YES	1.786	3.56
67	10076635	72	M	89	174	29.4	94	190	199	160	110	22	144	113	69	9.6	12	YES		6.9665	13.92
68	10083532	72	M	60	154	25	96	220	278	140	90	33	127	201	145	9.8	10	YES		15.906	31.8
69	10077841	74	M	68	169	23.8	88	177	180	180	90	11	254	58	3	10	12	YES		2.0895	4.178
70	10080418	48	M	59	162	22.9	82	188	226	140	90	28	57	91	53	11	2	YES		0.879	1.74
71	10063668	71	F	72	158	25.5	90	227	245	160	90	27	320	163	92	11	10	YES		3.901	7.802
72	10081925	58	F	64.3	167	23.1	93	287	340	140	90	33	306	163	94	11	8	YES		13.5835	27.16
73	10081960	54	M	84	172	28.4	102	189	190	150	100	28	193	150	84	11	4	YES		2.2075	4.4
74	10076723	69	M	80	176	25.8	93	178	241	160	100	32	161	219	162	11	15	YES		9.0415	18.08
75	10079411	48	F	59	154	24.9	98	308	298	140	90	40	11.4	94	39	11	5	YES		11.23	22.46
76	10075973	37	M	76	160	29.7	92	281	290	140	90	21	457	140	68	11	3	NO		42.579	85.14
77	10080092	61	M	80	164	29.7	102	221	234	150	90	10	584	150	22	12	10	YES	YES	13.732	27.46
78	10076316	84	F	78	156	32.1	102	206	244	140	86	26	162	121	73	12	20	YES		0.9945	1.98
79	10063053	46	M	63	167	22.6	92	231	276	150	90	27	88	118	70	15	5	YES		11.545	23.08
80	10081110	76	F	65	156	26.7	90	332	367	160	90	27	122	106	69	17	13	YES		2.8685	5.72
81	10073882	60	M	82	170	28.4	103	272	332	150	90	47	179	209	142	13	8	NO		22.95	45.8
82	10073928	63	M	65	170	22.5	92	110	111	150	90	23	32	39	11	5.4	0	NO		14.15	28.3
83	10075132	37	M	64	172	21.6	82	121	134	170	90	10	320	174	31	7.3	1	YES		15.15	30.3
84	10059614	56	M	72	162	27.4	88	121	154	120	80	34	320	154	83	5	0	YES		6.95	13.9
85	10071015	58	M	70	162	26.2	102	111	114	150	110	27	102	82	78	5	2	NO		10.05	20.1
86	10078928	72	M	96	169	33.6	104	110	123	140	90	42	111	81	53	5.8	8	YES		22.7	45.4
87	10070687	32	M	93	168	33	103	221	245	140	90	26	69	79	38	11	2	NO		5.65	11.3
88	10076505	60	F	68	156	27.9	84	248	308	140	90	41	140	136	60	11	8	NO		21.65	43.2

89	10082252	59	M	88	170	30.4	88	172	167	160	90	24	103	124	84	8.8	7	YES		15.3	30.6
90	10072962	63	M	65	176	21	103	146	156	150	90	50	127	165	108	9.6	4	YES		21.4	42.8
91	10079866	80	F	67	154	28.3	89	142	187	150	100	44	88	142	78	6.8	8	YES		7.92	15.84
92	10075988	54	M	92.2	170	31.8	114	146	145	150	100	14	189	110	66	7.8	6	YES		19.92	39.84
93	10050006	45	M	87	162	33.2	90	226	222	140	90	47	73	158	117	6.7	5	YES		1.85	3.7
94	10072802	59	F	66	157	26.8	90	206	230	160	90	43	93	108	56	6.1	10	YES		5.4	10.8
95	10075168	70	M	68	166	24.7	88	142	145	180	90	17	270	140	78	8.7	20	NO	YES	5.3	10.6
96	10082313	54	F	79.2	170	27.4	108	218	260	130	90	43	327	220	132	13	6	YES	YES	4.25	8.5
97	10074854	45	M	88	170	30	105	88	102	140	100	16	157	108	59	4.3	0	YES		4.75	9.5
98	10076063	56	F	73	158	29.2	88	123	127	130	100	26	215	97	34	6.7	5	YES		1.55	3
99	10081786	70	F	64.8	161	25	92	127	130	160	90	35	111	154	98	6	12	YES		7.55	15
100	10072235	59	F	74	156	30.4	110	152	160	160	90	51	98	183	119	10	5	YES		15.85	31.6
101	10079411	48	F	59	154	24.9	98	308	312	160	90	40	11.4	94	39	11	5	YES		1.7	3.4
102	10075992	48	F	88	155	36.6	117	306	430	160	90	15	170	84	33	14	2	NO		15.6	31.2
103	10064332	57	F	76	163	28.6	90	106	134	150	90	36	129	139	82	4.6	5	YES		1.79	3.58
104	10063506	63	F	73	156	30	94	112	118	140	90	27	93	92	51	6.9	10	YES		4.67	9.34
105	10074519	41	M	85	164	31.6	98	111	112	150	90	34	356	206	126	5.2	0	YES	YES	6.65	13.3
106	10070676	68	M	84	170	29.1	92	128	133	130	90	11	305	154	20	7.3	5	YES		20.9	41.8
107	10074616	49	M	89	170	30	104	270	287	150	100	53	79	120	56	12	15	YES		25.95	51.9
108	10076900	63	M	55	163	20.7	93	302	389	140	100	44	128	128	54	10	6	YES		7.25	14.5
109	10081230	58	F	63.8	157	25.9	92	155	233	150	90	45	206	215	128	13	4	YES		17.8	35.6
110	10079899	70	F	68	152	29.4	90	282	245	150	90	48	130	162	90	8.1	6	YES		3.05	6.1
111	10072649	50	M	54	170	18.7	83	126	124	140	90	27	199	157	95	6.2	3	YES		0.87	1.74
112	10073475	58	M	68.9	174	22.8	92	178	212	140	90	19	126	168	120	9.1	5	YES		7.63	15.26
113	10072799	43	M	69	158	27.6	92	198	200	150	90	43	232	203	131	12	6	NO		6.15	12.3
114	10075760	62	F	66	157	26.8	98	202	255	170	100	21	194	117	63	8.1	8	YES	YES	8.2	16.4
115	10076396	53	F	76	154	32	108	126	143	140	90	35	180	192	135	6.3	1	YES		9.65	19.2
116	10080613	60	F	65.7	152	28.4	84	163	198	150	110	27	233	144	97	9.1	1	YES		0.55	1.1
117	10076665	78	M	60	170	20.8	94	112	116	140	90	32	218	171	92	5.5	0	YES		9.45	18.9
118	10074623	58	M	70	168	24.8	91	112	118	140	90	31	42	82	31	5.5	2	YES		1.48	2.8
119	10071493	67	F	44	151	19.3	90	260	245	140	100	33	36	57	14	10	1	YES	YES	15.9	31.8
120	10072825	29	M	74	162	28.2	94	99	104	160	100	15	370	182	130	5.2	0	NO		6.76	13.4