STUDY TO ANALYZE THE ASSOCIATION OF CORTISOL LEVEL AND PREVALENCE OF CORONARY ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.

Dissertation submitted in partial fulfillment of regulation for the

award of M.D. Degree in General Medicine (Branch I)

The Tamilnadu

Dr. M.G.R. Medical University

Chennai

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CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr.ARYAMOL.M.K*** *and submitted in partial fulfillment of the requirements for the Degree of M.D., General Medicine, Branch I of The Tamilnadu Dr. M.G.R. Medical University, Chennai.*

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DECLARATION

I solemnly declare that the dissertation titled **"STUDY TO ANALYZE THE ASSOCIATION OF CORTISOL LEVEL AND PREVALENCE OF CORONARY ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS"** was done by me from September 2009 to September 2010 under the guidance and supervision of **Professor Dr.M.RAVEENDRAN M.D.**

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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CONTENTS

Introduction

INTRODUCTION

Type 2 diabetes is the predominant form of diabetes worldwide, accounting for 90% of cases globally. An epidemic of Type 2 diabetes is underway in both developed and developing countries. Globally the number of Type 2 DM is expected to rise from the current estimate of 150 to million in 2010 and 300 million in 2025. So Type 2 DM has become one of the world's most important public health problems. DM both insulin dependent and non-insulin dependent is a risk factor for CAD, accounting for 14%- 50% of new cases of CAD. CAD is the most common cause of death in adults with DM. In diabetes the incidence of CAD relates to the duration of DM, level of glycemic control and its pathogenesis involve endothelial dysfunction and Increased lipoprotein peroxidation, increased inflammation, prothrombotic state and associated metabolic abnormalities. [19]Increased activity of hypothalmopituitary axis and elevated cortisol level may underlie metabolic syndrome and coronary artery disease in patients with Type 2DM. People with Type 2DM are at increased risk of cardiovascular disease risk and hyperactive hypothalmopituitary axis thus suitable for study of association of cortisol level with cardiovascular risk[6].

Aims & Objectives

AIM OF STUDY

To analyze the association of Cortisol level and prevalence of coronary artery disease in patients with TYPE 2 DIABETES MELLITUS.

Review of Literature

REVIEW OF LITERATURE

Diabetes Mellitus

DM is characterized by chronic hyperglycemia, with the disturbance of fat, protein metabolism resulting from defects in insulin secretion, action or both. When fully expressed DM is characterized fasting hyperglycemia but disease can also be recognized during less overt stages most usually by presence of glucose intolerance. Effects of DM include long term damage, dysfunction and failure of various organs especially eyes, kidneys, heart and blood vessels. DM may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss and polyphagia. In its most severe forms with ketoacidosis or non ketotic hyperosmolarity which is in the absence of effective treatment leads to stupor, coma and death[3].

Clinical Stages

Individuals who ultimately develop DM pass through several clinical stages during its development, initially glucose regulation is normal and no abnormality of glycemia can be identified even if this individuals undergo an oral glucose tolerance test.This stage is followed by period of variable duration in which glucose regulation is impaired.Diabetes itself is characterized by either fasting glycemia or marked abnormalities of glucose tolerance or both. If insulin is required to prevent ketosis such patients are designated as insulin dependent diabetes. In all forms of DM there may be remission in the extent of hyperglycemia patient may revert to have impaired glucose regulation or even normal glycemia, particularly if diabetes is recent in onset. Gestational diabetes is often followed by impaired glucose tolerance following parturition and a variable period such women may be normoglycemic with subsequent pregnancy gestational diabetes is likely to recur. Many women who have had GDM develop diabetes within few years.

Type 2DM is the most common form of diabetes. It is characterized by disorders of insulin action and secretion either of which may be the predominant feature. Usually both are present at the time diabetes become clinically manifested although specific etiology of this form of diabetes is not known although, autoimmune destruction of beta

cells does not occur. The patients with Type 2DM usually have insulin resistance and relative rather than absolute insulin deficiency. At the time of diagnosis of diabetes and often throughout there lifetime in these patients do not need insulin treatment to survive, although ultimately many require it for glycemic control.Most patients with diabetes are obese and they develop diabetes and obesity aggravates the insulin resistance. Type 2DM frequently goes undiagnosed or many years because hyperglycemia develops gradually and in the earlier stages it is not severe enough to produce classic symptoms of diabetes ,however such patients are at increased risk of developing micro vascular and macrovascular complications. There circulating insulin may be normal or elevated yet insufficient to control blood glucose levels within normal range because of the insulin resistance. Insulin resistance may improve with weight reduction or pharmacological treatment and results in normalization of patients glycemia. The risk of developing type 2DM increases with age, obesity and physical inactivity. Type2DM shows strong familial aggregation so that person with a parent or sibling with disease are at increased risk, as are individuals with obesity, SHT, Dyslipedemia and women with history of gestational diabetes. The frequency of Type 2DM varies considerably among different racial or ethinic sub groups. Persons of native Americans, Polynesians,Micronesian ,Asian Indians, Hispanics or African Americans

descent are at higher risk than persons of European Origin. Although the disease is most commonly seen in adults, the age o onset tends to be earlier in persons of non-European origin[3].

Epidemiology of Diabetes Mellitus

The number of persons in a particular place at a particular time who have DM, expressed as a proportion, this number is commonly called the prevalence rate or preferably the prevalence. The incidence rate is the number of new cases. The rate of type 2 DM is increasing steadily with age,with an almost 100 fold increase from early childhood to old age. There are two peaks of occurrence o Type I DM. one centered in 2nd decade and other in the 6th and 7th decades.Type one diabetes have considered the disease occurrence in children,typically under the age of 15 years.Type I DM rarely occurs during the 1st year of life. The incidence rises sharply until the age of 12 to 14 years and then declines. The incidence of Type I DM with onset after the age of 30 years are rare[4].

Insulin Resistance

Generally refers to the resistance to the metabolic effects of insulin, including suppressive effects of insulin on endogenous glucose production,

stimulatory effects on peripheral glucose uptake and glycogen synthesis, inhibitory effects of insulin on adipose tissue lipolysis. The mortality and morbidity of Type 2 DM associated with insulin resistance. Insulin resistance predates the onset of Type 2 DM by 10-12 years and is the best clinical predictor of subsequent development of Type 2 DM[4].

Metabolic Syndrome

Reaven formally recognized the clinically significant association between insulin resistance and cardiovascular risk actors. NCEP and ATP III in 2001 gives criteria as plasma glucose levels more than 110 mg/dl, visceral Obesity (more than 35 inches in women, more than 40 inches in men), SHTN(130/85 mm of Hg),Hypertriglyceridemia more than 150 mg /dl, HDL less than 40 mg/dl in men and less than 50 mg/dl in women, 3 of the following criteria fulfills metabolic syndrome. Other recognized syndrome include systemic inflammation, a prothrombotic state, increased oxidant stress. Increased circulating levels of TNF alpha, IL-6 and other pro inflammatory cytokines may contribute to some of the metabolic features of metabolic syndrome , whereas increased levels of Plasminogen Activator Inhibitor – 1(PAI-1) appears to heighten the risk of atherothrombosis. Increased risk of atherosclerotic disease mortality and morbidity is conferred by metabolic syndrome[4].

Maturity Onset Diabetes Mellitus

By definition, a family is considered to have early onset diabetes if at least one and ideally two members of family are diagnosed with diabetes before the age of 20. Patient are considered non insulin dependent I if 5 years after the diagnosis they either are not receiving Insulin treatment or are insulin treated but have significant levels of circulating C-Peptide. Autosomal dominant inheritance beta cell dysfunction rather than insulin resistance is characteristic of MODY. Subjects with MODY mutation do not need to be obese to develop diabetes, in marked contrast to early onset type 2DM.

Type 2DM and epidemic of CAD

Type 2 DM is multifactorial disease and shows heterogeneity in numerous respects. Type 2DM is a descriptive term and manifestation include metabolic syndrome, cluster of CAD risk factors, glucose intolerance , hyperinsulinemia,dyslipidemia , SHT, visceral Obesity , hypercoagulability and microalbuminuria[4].

Mechanisms for microvascular pathology in Diabetes

The partial loss of insulin effects due to dysfunction or the destruction of beta cells or peripheral insulin resistance and ensuing hyperglycemia and other disturbance of metabolism have profound consequence on cellular function , Extracellular matrix , organ function and whole body physiology. Microvascular dysfunction and pathology may be initiated by hypertension. The glomerular hypofilteration observed in DM may be caused in part by systemic Hypertension. Mechanism that has been described that link mechanical forces to vascular dysfunction including pressure, stretch and shear stress. Overactivity of sympathetic nervous system can be a participating factor in the development of hypertension in both Type 2DM. Insulin is thought to have vasoconstrictor effects through activation of sympathetic nervous system[(5)].

Modification of extracellular and intracellular proteins by sugars can result in formation of AGEs, which is virtually irreversible. The most prevalent AGE is carboxy methyl lysine. Because of there long turnover rate structural extracellular protein such as collagen are particularly susceptible to AGE modification. AGE has been demonstrated in numerous tissues in both types of diabetes, such as retina and the

glomeruli. AGEs may interfere with vascular signaling by facilitating breakdown nitric oxide.AGE may impair the functioning of intracellular protein as in the case of reduced activity of basic fibroblast growth factor in endothelial cells. AGE also alters the properties of extracellular matrix. Glcosylation of collagen type IV renders it resistant to degradation by MMP. AGE crosslinking of type I collagen expands the packing of collagen molecules. Modification of type IV collagen decreases endothelial cell adhesions. Stimulation of AGE receptor can lead to trans differentiation of renal tubular epithelial cells to myofibroblasts, Which may be responsible for accumulation of extracellular matrix.

Typical elements of inflammatory process are evident in the vasculature of diabetes. Increased expression of vascular adhesion molecules leading recruitment of leucocytes to vascular walls is regarded as pivotal event in early inflammation. Blocking intracellular adhesion molecule-1(ICAM-1) prevents leukostasis and retinal leakage. The proinflammatory cytokine TNF-alpha is also important in pathology[5].

Pathogenesis of cardiovascular disease in Diabetes Mellitus

DM is a major independent risk factor for cardiovascular disease. Increased prevalence of CAD in diabetes has been attributed in large part to the acceleration of coronary atherosclerosis, which occurs at an earlier age and advances more rapidly to clinical cardiovascular events in individuals with diabetes than those without diabetes. The patients with diabetes are also prone to arterial thrombosis due to persistently activated thrombogenic pathway and impaired fibrinolysis. Histopathological study of atherotomy specimen from diabetic patients showed two fold increase in PAI-1 and decrease in the level of immunoreactive urokinase Plasminogen activator. Macrophage infiltration also elevated nearly two folds. Morphometric analysis of coronary atherectomy specimen from primary lesions has indicated that relative amounts of collagen rich and hypercellular plaque components, which comprised approximately 90% of the total area were similar in DM and non DM subjects. Coronary artery calcification in diabetic subjects appears either similar or increased compared to that in non diabetic subjects. The atherogenic effects of diabetes and insulin resistance appaears to be initiated by combination of metabolic abnormalities related to hyperglycemia , impaired insulin action or insulin deficiency , a prothrombogenic dyslipedemia and comfounding factors such as hypertension and obesity. Vasoactive

hormones, cytokines and growth factors such as angiotensin II , TNF-alpha and vascular endothelial growth factor amplify and in part mediate the adverse vascular effects of these metabolic abnormalities . The metabolic and hormonal imbalance can induce endothelial dysfunction, vascular inflammation, intimal lipid accumulation, fibrosis and hypercoagulability leading to atherosclerosis and thrombosis.

Thrombosis is the major cause of stenosis and sudden death. Intramural arterial thrombosis can be triggered by the disruption of complex plagues, which expose the blood to thrombogenic factor that are enriched in the sub endothelial area. The tissue factor the major activator of the extrinsic coagulation pathway is highly expressed in the plague core. Disruption of the plaque surface allows this tissue factor to bind circulating factor VII in the blood to activation of coagulation cascade and formation of clot. Elevated levels of tissue factor in vascular tissues in diabetic and obese insulin resistant patients may predispose to the activation of coagulation cascade. More over increased arterial expression of PAI in diabetes may impair the dissolution of nascent thrombi.

Diabetes has number of adverse effects on vascular endothelium that impair these functions and likely to facilitate atherosclerosis and thrombosis. Diabetes increases the expression of leukocyte adhesion

molecules that mediate binding and the infiltration of monocytes into the arterial subendothelial space. Diabetes impairs endothelial barrier functions which increase transendothelial permeability and access of circulating molecules to vascular interstitium. Diabetes also alters the endothelial cell synthesis of a host of vascular hormones and factor that affect vascular tone, hemodynamics and coagulation.

Arterial stiffness is strongly associated with atherosclerosis. Increased glycation of ECM proteins such as collagen and elastin may increase covalent intermolecular cross linking and there by reduce elasticity. Increase arterial stiffness may also result from arterial calcification, arterial wall thickening or increased chronic vascular smooth muscle cell contraction due to an imbalance in vasoactive hormone activities. Impaired arterial elasticity might contribute to atherogenesis by increasing mechanical and shear forces causing endothelial damage, activation stretch activated mechanoreceptors and increased release of trophic factors.

Hyperglycemia, plasma insulin and insulin resistance, elevated lipids and lipoprotein , circulating adhesion molecules, elevated Plasminogen activator inhibitor-1, C-reactive protein, fibrinogen,

hyperhomocystenemia ,hypertension all contribute to CAD in type II DM[6].

Cortisol

Three mains type of hormones are produced by adrenal cortex, glucocorticoids(cortisol,corticosterone),minerelocoticoids(aldosterone,de oxycorticosteroids) and sex steroids. All steroids hormones are derived from the cyclopentanoperhydrophananthrene structure that is 3 cyclo hexane rings and single cyclopentane ring. Glucocorticoids are secreted in relatively high amounts (cortisol 10-20 mg/day) from zona fasciculata of adrenal cortrex under the control of ACTH. Classical endocrine feedback loops are in place to control the secretion of both hormones. Cortisol inhibits the secretion of CRH and ACTH form the hypothalamus and pituitary respectively. Aldosterone induced sodium retention inhibits renal rennin secretion.

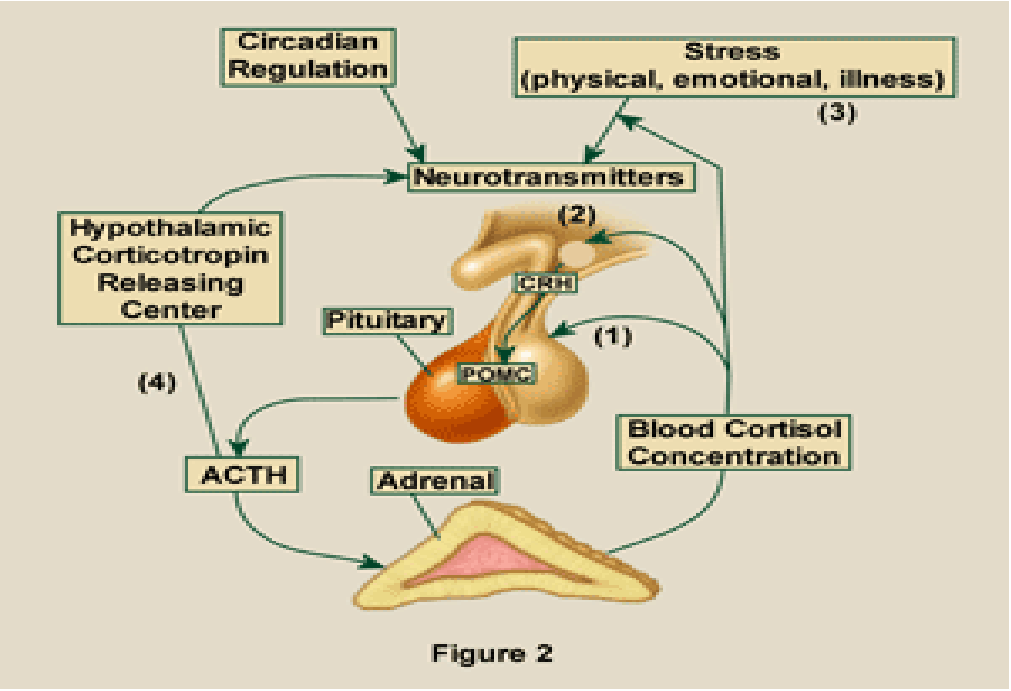

Circadian Regulation
Stress (physical, emotional, illness)
(3)
Neurotransmitters
(2)
Hypothalamic Corticotropin Releasing Center
CRH
Pituitary
(1)
POMC
(4)
Blood Cortisol Concentration
ACTH
Adrenal

Figure 2

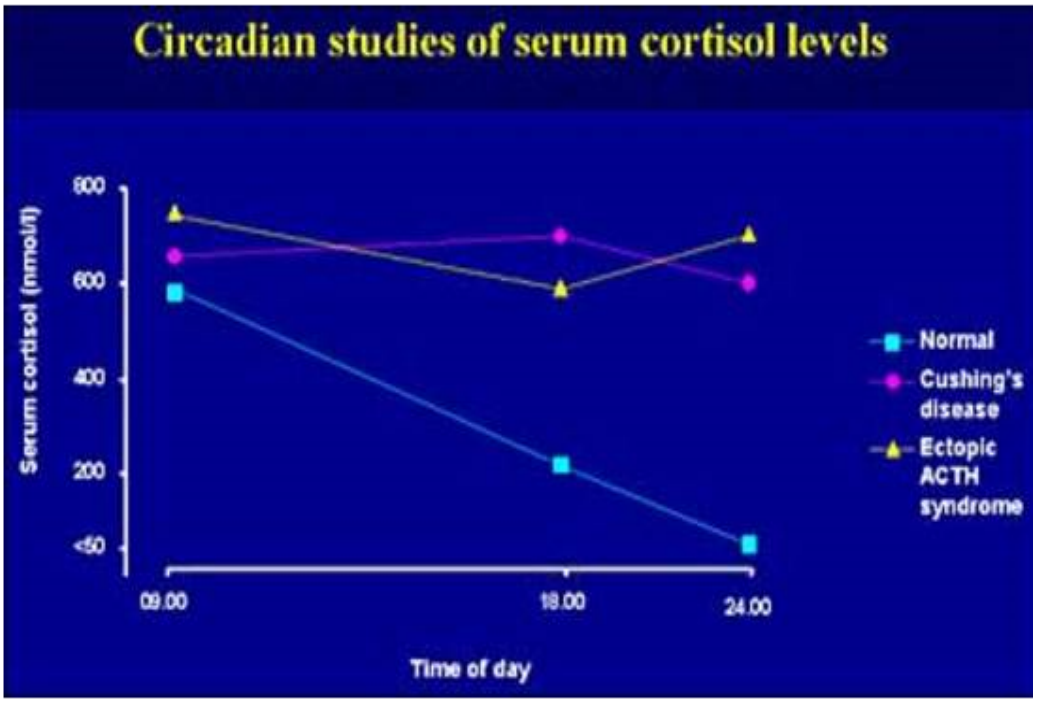
Effects of Glucocorticoids

Glucocorticoids increase blood glucose concentration through their action on glycogen, protein and lipid metabolism . In the liver cortisol stimulates glycogen deposition by increasing glycogen synthase, and inhibiting glucogen mobilizing enzyme glycogen phosphorylase. Hepatic glucose output increases throughactivation of key enzyme involved in gluconeogenesis, principally glucose 6-phosphatase and phosphoenol piruvate carboxy kinase. In peripheral tissue cortisol inhibit glucose uptake and utilization .in adipose tissue lipolysis is activated, resulting in the release of free fatty acids in to the circulation .

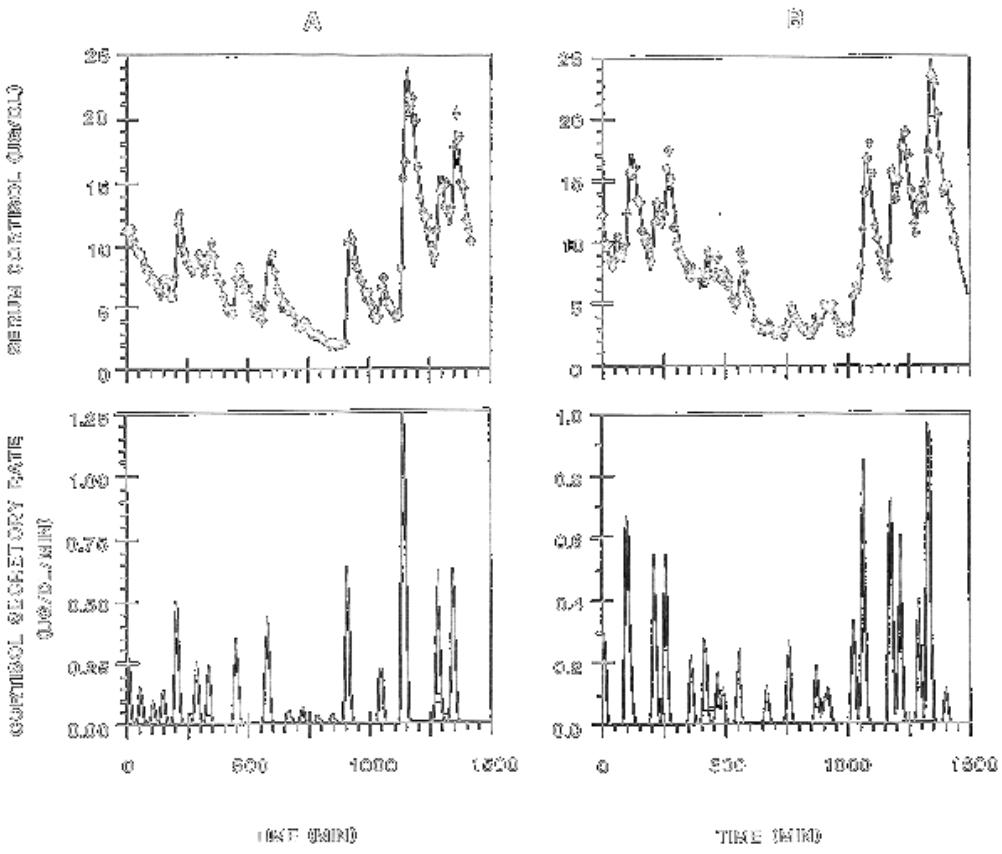
An increase in the circulating cholesterol and triglycerides observed but HDL cholesterol levels falls. Glucocorticoids also have permissive effect on other hormones incuding catecholamines and glucagone . the resultant effect to cause insulin resistance and an increase in blood glucose concentration at the expense of protein and lipid catabolism[7].

Normal Pulsatile Secretion of

Cortisol



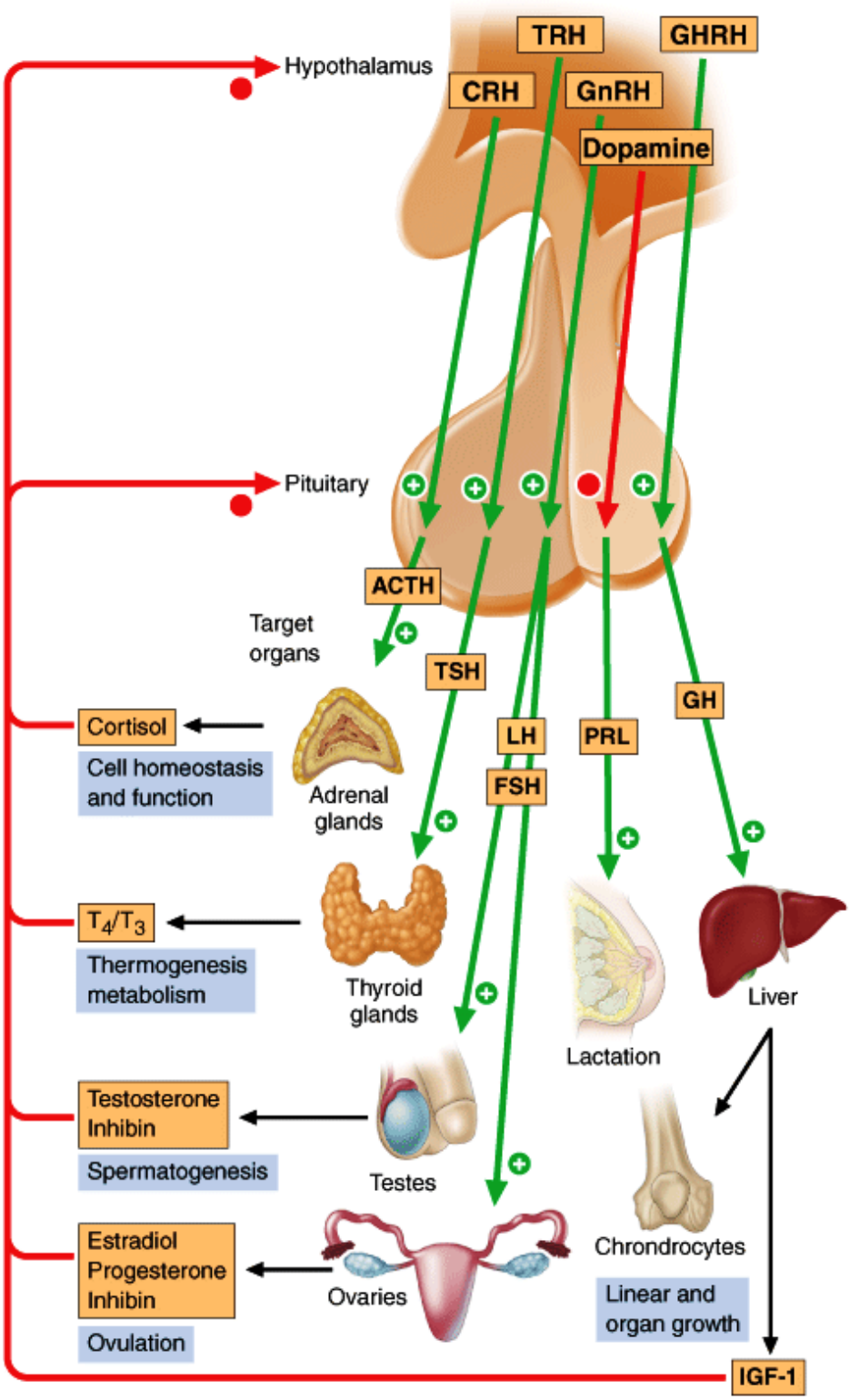
Cortisol in Normal Individual



The hypothalamo-pituitary-adrenal axis

ACTH is the principle hormone stimulating adrenal corticoid biosysthesis and secretion.ACTH has 39 aminoacid sequence synthesized within anterior pituitary. ACTH secretion is tightly controlled by numerous factors; notably CRH and AVP (argeninvasopressin). Additional control is provided by an endogenous circadian rhythm, stress and feedback inhibition by Cortisol itself. CRH is a 41 amino acid that is synthesized in the hypothalamus and act on anterior pituitary to secrete ACTH[(7)].

The hypothalamo-pituitary-adrenal axis



The proinflammatory cytokines notably IL-1,IL-6 and TNF alpha also increase ACTH secretion either directly or by augmenting the effect of CRH. Leukemia inhibiting factor a cytokine of IL-6 family is a further activator of HPA axis. This explains the response of HPA axis to an inflammatory stimulus, and is an important immune endocrine interaction. Physical stress increases ACTH and cortisol secretion again through central action mediated via CRH and AVP.Cortisol secretion rises in response to fever, surgery , burn injuries, hypoglycemia, hypotension and exercise,this can be viewed as a normal counter regulatory response to an insult. Depression is associated with high circulating Cortisol concentrations. The mechanism underlying elevated Cortisol level in diabetes is not known. Corticosteroid binding globulin levels are not elevated in diabetes[7].

Coronary artery disease

CAD is the most common form of heart disease.

It's a spectrum of disease ranging stable angina, unstable and myocardial Infarction. Symptom complex may occur whenever there is an Imbalance between myocardial Oxygen supply and demand. Coronary atheroma by far the most common cause of angina although the symptom may be a manifestation of other forms

of heart disease particularly aortic valve disease and hypertrophic cardiomyopathy.

Atherothrombosis is no longer considered as a disease of developed world because myocardial Infarction and stroke are increasingly prevalent worldwide. By 2025 cardiovascular mortality on a worldwide scale will be surpassed that of every major disease group.

From an epidemiological point of view a risk factor is a characteristic or feature of an individual or population that is present in early life and is associated with an increased risk of developing future disease[9].

The risk factor of Interest may be:

1. Acquired behavior (smoking)
2. Inherited trait (Familial Hyperlipedemia)
3. Laboratory value (Cholesterol, C Reactive protein)

For a risk to have clinical usefulness the marker of interest must predate onset of disease. Several risk factors such as Hyperlipedemia and hypertension are modifiable. Trial has demonstrated that lowering these factors reduces vascular risk. Although it

remains controversial, whether markers of inflammation are directly or indirectly associated Atherothrombosis, several inflammatory markers have proved highly effective in clinical practice for evaluating vascular risk. Not all coronary events occur in individuals with traditional risk factors. In some individuals abnormalities of inflammation,haemeostasis / thrombosis appears to contribute decisively nearly half of MI and stroke occur among individual among Hyperlipedemia.

Risk Factors

The role and relative importance of many risk factors for the development of coronary, peripheral and cerebro vascular disease have been defined in animal studies and clinical interventional studies. The effect of risk factors is multiplicative rather than additive. People with combination of risk factors are at greatest risk so assessment should take account of all identifiable risk factors[9].

Conventional risk factors

1. Age/ Sex
2. Family History
3. Smoking
4. Hypertension
5. Hypercholestrolemia
6. Diabetes mellitus
7. Hemostatic factors
8. Physical activity
9. Obesity
10. Alcohol
11. Other dietary Factors
12. Personality
13. Social deprivation
14. Mental stress[1]

Age and Sex

Age is the most powerful independent risk factor for CAD. Premenopausal women have lower risk of disease than men although this sex difference disappears after the menopause. Hormone replacement therapy has no role in the primary or secondary prevention of CAD. Isolated estrogen therapy may cause an increased cardiovascular event rate.

Family History

CAD disease often runs in families due to combination of shared genetic, environmental and life style factors. The most common inherited risk characteristics are polygenic. A positive family history is present when clinical problems in first degree relatives occur at relatively young age such as less than 50 years for men and less than 55 years for women.

Smoking

Probably the most important avoidable cause of CAD. There is strong consistent and dose linked relationship between cigarette smoking and CAD, especially In younger individual less than 70 years. 35%-40% of all smokers die due to coronary artery disease. Persons who consume 20 or more cigarette daily have a 2 to 3 fold increase in CAD.

Consumption of as few as one or four cigaretts daily increase chance of coronary artery disease, such light level of smoking have a major impact on myocardial infarction and all cause mortality.

Hypertension

The incidence of CAD increases as BP rises, as this excess risk is related to both systolic and diastolic BP as well as pulse pressure. Anti hypertensive therapy reduces cardiovascular mortality, stroke and heart failure.

Hypercholestremia

Risk increases with increase in serum cholesterol concentrations. Lowering serum cholesterol concentration reduces the risk o f CAD.

Hypercholestrolemia ,increased level of LDL and reduced HDL increased risk of CAD.

Diabetes Mellitus

Potent risk factor accounting for 40%-50% of new cases of CAD. CAD is the most common cause of death in adults with DM. Insulin resistance is associated with obesity and physical inactivity is an important risk factor. Hypothalamic pituitary adrenal hyper activity may underlie metabolic syndrome. New literatures postulate that elevated cortisol may be a sole risk factor for CAD[19].

Haemostatic Factors

Platelet activation and high levels of fibrinogen are associated with increased risk of coronary thrombosis. Antiphospholipid antibodies are associated with recurrent arterial thrombosis.

Physical Inactivity

Physical inactivity roughly doubles the risk of CAD and is a major risk factor for stroke. Regular exercise has a protective effect which may be related to increased HDL level lower BP and collateral vessel development.

Obesity

Obesity, particularly central or truncal in an independent risk factor. It is often associated with other adverse factors such as hypertension, diabetes and physical inactivity, hyperlipidemia.

Alcohol

Alcohol consumption is associated with reduced rate of CAD. Excess alcohol consumption is associated with hypertension and cerebrovascular disease.

Other dietary Factors

Diet deficient in fresh fruits vegetables and PUFA are associated with increased risk of CAD. The introduction of Mediterranean style diet reduces CAD. Dietary supplements such as Vit C, Vit E, Beta-carotene, Folates and fish oils don't reduce CAD and some cases have been associated with harm.

Personality

Certain personality traits are associated with increased risk of CAD. Nevertheless there is little or no evidence to support the popular belief.

Many patients with coronary artery disease seems to be compulsive driven, over achievers who are unable to relax and are quick to feel angry and frustrated when things do not proceed as planned. Those with type A behavior had significantly elevated rate of developing coronary artery disease in 5- 8 years follow up. Type B personality is unhurried , less aggressive and do not get upset when thwarted and have less chance of CAD[(9)].

Social deprivation

Health inequalities are a major cause of CAD. The impact of established risk factors amplified in patients who are socially deprived the current guidelines recommended that treatment thresholds should be lowered for them.

Mental stress

Both depression and mental stress predispose to CAD. Adrenergic stimulation of mental stress can augment myocardial oxygen requirements and aggravate myocardial ischemia. Mental stress can cause coronary vasoconstriction particularly in atherosclerotic coronary arteries and hence can influence myocardial oxygen supply. Depression may cause over activity of HPAA[(9)].

Depression

Depressed Patients show hyper reactivity of HPAA and hyper cortisolemia and cortisol have atherogenic effects due to activation of pro inflammatory cytokines such as TNFalpha and IL-6 which may accelerate atherosclerosis. While acting classically as an antiinflammatory hormone cortisol excess can promote inflammation and accelerated atherosclerosis by producing insulin resistance changes in corticosteroid binding protein and regulation of pro inflammatory cytokines[(7)].

CAD Clinical Spectrum

- ❖ Stable angina
- ❖ Unstable angina
- ❖ Myocardial Infarction
- ❖ Heart failure
- ❖ Arrhythmia
- ❖ Sudden death

Investigations

- ❖ Resting ECG
- ❖ Exercise ECG (Exercise tolerance test (ETT))
- ❖ Treadmill
- ❖ Myocardial perfusion scanning
- ❖ Coronary arteriography
- ❖ Stress echo cardiography

Management

General Measures

Carefully assess extent and severity of arterial disease , identify riskfactors such as smoking, hypertention , and hyperlipidemia .patient should be admitted urgently in case of MI and unstable angina because there is significant death rate or recurrent myocardial ischemia during the early unstable phase, and appropriate medical therapy can reduce the

incidence of these by 60% . patients are usually managed in a dedicated cardiac unit where necessary expertise, monitoring, and resuscitation facilities can be concentrated. If there is no complications , the patient can be mobilized from the second day and dischargedfrom hospital after3-5 days.

Antiplatelet therapy

In MI oral administration of 75- 300mg of aspirin improves survival ,with a 25% of relative risk reduction in mortality . first dose should be given orally within 12hours and therapy should be continued indefinitely if there is no side effects.

Analgesia

Adequate analgesia is essential not only to relieve distress but also lower adrenergic drive and there by reduce vascular resistance,BP, infarct size and susceptibility to ventricular arrhythmias.

Antianginal drug treatment

Sublingual glyceryl trinitrate 300- 500 micro gram is a valuable first aid measure in MI, which relieve pain ,reduce arrhythmia and improve short term mortality in patients who present within 12hours of the onset of symptoms. It should be avoided if there is hypotention or bradycardia.

Trombolysis

Promt trombolytic therapy within 12hours and particularly within 6hours ,of the onset of symptoms reduces mortality in patients with acute MI.

Invasive Treatment

- Percutaneous Coronary Intervention
- Coronary Artery Bypass Grafting

Lifestyle and risk factor modification

Smoking

5 years mortality of patients who continue to smoke cigarette is double that of those who quit smoking at the time of their acute coronary syndrome. Giving up smoking is the single most effective contribution of a patient can make to his or her future. The success of smoking cessation can increase by supportive care and pharmacological therapy.

Hyperlipedemia

HMGCoA reductase enzyme inhibitors can produce marked reduction in total cholesterol and reduce the subsequent risk of death, reinfarction, stroke and the need for revascularization.

Mobilization and rehabilitation

Necrotic muscle of an acute MI takes 4 -6 weeks to be replaced by fibrous tissue and it is conventional to restrict physical activities during this period. When there is no complications the patient can mobilize on 2nd day, return home in 3-5 days and gradually increase activity with the aim of returning to work in 4-6 weeks. Emotional problems such as denial, anxiety and depression are common and must be addressed. Many patients are severely and even permanently incapacitated as the result of psychological rather physical effects of MI and all benefits from thoughtful explanation, counseling and reassurance at every stage of illness. Many patients mistakenly believe that stress was the cause of their heart attack and restrict their activity inappropriately. The patients spouse or partner will also require emotional support, information and counseling. Formal rehabilitation programs based on graded exercise protocols with individual and group counseling are often very successful and in some cases have been shown to improve long term outcome[1].

Secondary prevention drug therapy

Aspirin and clopidogrel

Low dose aspirin herapy reduces the risk of further infarction and other vascular events by approximately 25% and should be continued indefinitely if there are no unwanted effects, clopidogrel should be given in combination with aspirin for atleast 3 months.

Beta blockers

Continuous treatment with an oral beta blocker reduces the longterm mortality by approximately 25% among the survivors of acute MI . a minority of people do not tolerate beta blockers because of brady cardia, AVblock , hypotention , or asthma.

ACE Inhibitors

Several clinical trials have shown that longterm treatment with ACEInhibitors can counteract ventricular remodeling, prevent onset of heartfailure, improve survival, reduce recurrent MI and avoid rehospitalization. Benefits are greatest in those with overt heart failure.

Cortisol secretion in patients with Type 2 DM (relationship with chronic complications) - American Diabetes association

In Type 2 diabetes subject's cortisol secretion is associated with complication and metabolic control of diabetes. In the related study ADA evaluated 170 Type 2 Diabetic subjects, the presence of chronic complication like incipient nephropathy, asymptomatic neuropathy, silent macro angiopathy and hyperactivity of HPAA. The end of the study concluded that in Type 2 DM patients HPAA activity is enhanced and degree of cortisol secretion is related to the presence and number of diabetes complications. In patients with type 2 DM glucocorticoid secretion has been suggested to be a possible link between insulin resistance and features of metabolic syndrome (HT, Obesity, CAD, Hyperlipedemia and

Type 2 DM). While glucocorticoid excess has been demonstrated to lead to diabetes or worsen metabolic control the relationship between cortisol level, insulin resistance and chronic complications in Type 2 DM patient's hypercorticolism is a matter of debate. In diabetic subjects without chronic complications HPAA axis activity was comparable with that of non diabetic patient, whereas in diabetic subjects with chronic complications cortisol level was increased. A trend for higher cortisol

secretion in patients with either diabetic retinopathy or cardiovascular complication was found. Insulin resistance where comparable between diabetic subjects with or without diabetic complications and not associated with parameters of HPAA axis. So it is possible to speculate that an increased cortisol secretion may contribute to worsening the metabolic control of diabetes and insulin sensitivity. Possible effect of increased cortisol secretion in the pathogenesis of chronic diabetic complication is not mediated by insulin resistance. Further studies are needed to investigate possible causative role for cortisol secretion in the development of chronic complication of diabetes[10- 14].

Cortisol , Testosterone and Coronary Heart Disease (prospective evidence from the Caerphilly Study - American Heart Association

There is a popular belief that chronic stress causes heart disease through psyconeuroendocrine mechanism. Specific association between cortisol testosterone ratio and incidence of ischemic heart disease apparently mediated through insulin resistance syndrome. Whether this reflex effects of chronic stress behavioral factors or genetic influences remains to be determined.Neuroendocrine have been viewed as a central component of stress response. Stress suppresses testosterone levels which appear to be a consequence of cortisol elevation. Glucocorticoid suppresses testosterone in men and low testosterone levels are a central component of chronic physical and psychological stress response in men. A high ratio of cortisol and testosterone levels has been widely used as endocrinological indicators of stress in human studies. A higher cortisol testosterone ratio was associated with younger age, higher fibrinogen levels and smokers. More favorable socioeconomic position was associated with higher cortisol testosterone ratio. But it was not seen in parental social class. Among drinkers cortisol testosterone ratio increased with amount of alcohol consumed. CADmortality and incidence positively associated with cortisol testosterone ratio. There is no association of cortisol testosterone ratio withnon CADmortality in DM

patients. Cortisol is a potential mediator between stress and cardiovascular disease. Endogenous testosterone levels have also been related to fasting glucose and insulin concentration and can predict the onset of Type 2DM. Cortisol and testosterone secretion are inter related. Activation of HPAA not only results in an elevation of adrenal cortical steroids but also inhibit gonadotropin secretion. Cortisol testosterone ratio is associated with a specific elevation in CAD risk that was robust to the adjustments for potential confounding factors but appeared attributable to components of Insulin resistance syndrome. Evidence from various sources suggest that high cortisol and low testosterone levels are associated with worse profile of Insulin resistance components and modifications like testosterone supplementation improves this pattern. This suggests that methods of reducing CT ratio may improve Insulin resistance and reduce the risk of coronary arterial disease [15-16].

Correlation between HPAA and the metabolic syndrome

The metabolic syndrome has several similarities with Cushing Syndrome (impaired glucose tolerance, HTN, dyslipedemia, central Obesity) suggesting that abnormalities in the regulation of HPAA may have a link with metabolic syndrome. Several studies suggested an association between clinical signs of metabolic syndrome and increase HPAA activity based on increased cortisol concentration at 9 am and

increase cortisol response to corticotrophin. According to Barker hypothesis fetal malnutrition could determine adult cardiovascular disease and endocrine metabolic disorders (Obesity, type II DM, Hyperlipedemia). The suggested mechanism of phenomenon is that the suboptimal fetal nutrition results in glucocorticoid over production. The 11 beta hydroxyl steroid dehydrogenase is an important enzyme in cortisol metabolism. The increased expression of 11 beta hydroxyl steroid dehydrogenase in fat tissue could lead to central obesity and impaired glucose tolerance. The hypothesis that increase CRH production drives the over active HPAA was not proven[19].

Elevated Plasma Cortisol Concentration : A link between low birth weight and Insulin resistance Sydrome - Journal of Clinical Endocrinology and Metabolism

Recent studies have shown that reduced fetal growth is associated with development of Insulin resistance syndrome in adult life. The mechanism was not known however increased activity of HPAA may underlie this association. Studies in both Europe and North America have shown that low birth weight is associated with increased rates of CAD in adult life. It is well established that environmental exposure in prenatal and early post natal life may result in permanent modification of neuroendocrine modification of stress throughout life[17].

Circulating plasma cortisol concentration is not associated with coronary artery disease or peripheral vascular disease - Oxford Journal of Medicine (Qjm)

Study conducted to determine whether basal circulating cortisol level predict CAD or PVD. Background of this study was obesity epidemic with associated metabolic syndrome may increase the prevalence of cardiovascular disease. Conclusion of the study was single measurement of Cortisol is a poor predictor of vascular disease. More detailed charactrisation of the HPAA is necessary to determine the role of

circulating endogenous Glucocorticoids and there responsiveness to stress in atherosclerosis[18].

Elevated fasting plasma Cortisol is associated with ischemic heart disease and its risk factors in people with type 2diabetes : The Edinburgh Type 2 Diabetes Study

The Edinburgh Type 2 diabetes study is a prospective study investigating mechanism and risk actors for diabetes related cognitive decline and or the development and progression of micro and macro vascular disease in diabetes.

Context of the study was increased activity of HPAA may underlie metabolic syndrome but whether circulating plasma Cortisol level predict cardiovascular endpoint is less clear. Selected people with Type 2 DM are at increased risk of cardiovascular complication and thus are suitable to study the association of plasma Cortisol with cardiovascular risk. Elevated plasma Cortisol level measured in the morning has been described in the individuals with glucose intolerance, HTN and dyslipedemia. This has been associated with alteration in the regulation of the HPAA. In people with diabetes, early studies of HPAA regulation showed inconsistencies this was partially caused by inclusion of individuals with Type 1 DM. the summary and conclusion of study says the previously described association between HPAA activation and

metabolic syndrome are evident in people with Type 2 DM. Elevated plasma Cortisol are also associated with greater prevalence o ischemic heart disease in people with Type 2 DM[19].

Design Methodology Techniques

The study was conducted at Coimbatore Medical Hospital, Coimbatore during period of September 2009 to September 2010. 50 patients of Type 2DM were included in the study. No patients had been counted if he/she got admitted again after discharge during this period.

Design of study

- Cross sectional study

Methodology

50 Type 2DM patients who got admitted in Coimbatore Medical College, Hospital were included in the study. 50 consecutive were recorded.

In those patients BP, Waist Circumference, Blood Glucose Levels, Lipid profile, fasting cortisol level and Urine Protein were measured and ECG, Echocardiogram was taken to study whether there is an increased association of cortisol level with prevalence of coronary artery disease in patients with Type 2DM.

Why Type 2DM patients are involved in the study?

In Type 2DM the chance of CAD and hyperactive HPAA is more thus easy to study the association in these patients.

Inclusion Criteria

1. Type 2 DM Patients
2. Age group above 50 years
3. Both Sexes
4. First Admission

Exclusion Criteria

1. Cushing disease / Syndrome
2. Patients who are on steroid treatment
3. Age group below 50 years

Diagnosis of Diabetes Mellitus

1. Random Blood Glucose Concentration more than 200 mg %(>11.1mmol/L)
2. Fasting Glucose more than 126 mg % (>7mmol/L)
3. Two hour plasma glucose more than 200 mg %(>11.1mmol/L) during an oral GTT.

Dignosis of Coronary Artery Disease

1. Symptoms Like angina and anginal equivalents.
2. ECG
3. ECHO

ECG Recording:

12 lead ECG was taken or all the cases;It was standardized to produce deflection of 10mm/1mvolt in put and paper speed was set 25 mm / sec. Changes of for coronary artery Disease were noted. It includes

1. T Wave changes
2. ST changes
3. Bundle branch block

ECHO Cardiography
M MODE 2D ECHO was done in all patients.

1. Rhythm of Heart noted

2. Regional wall motion abnormality

3. Papillary muscle dysfunction

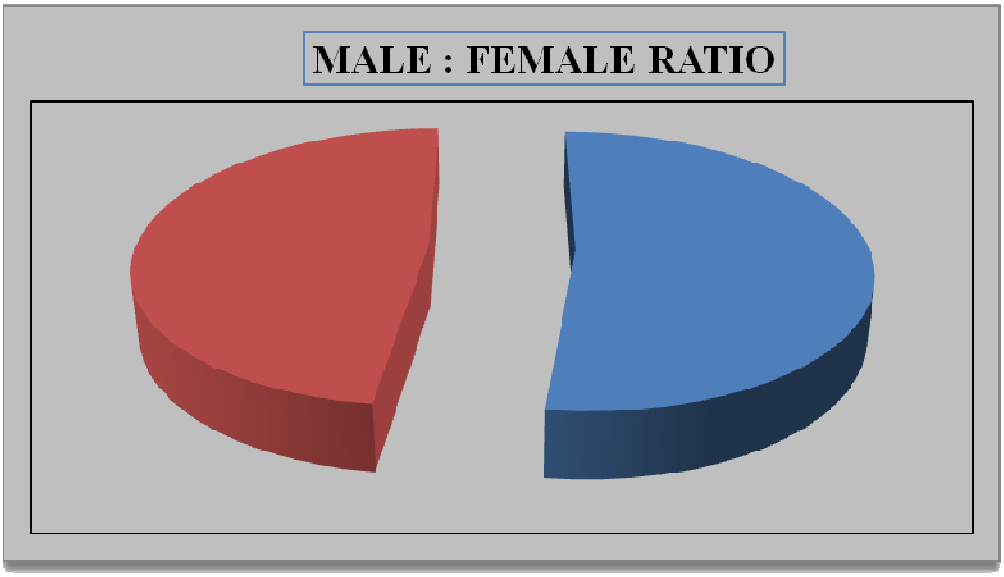
4. Systolic / Diastolic function

CORTISOL MEASUREMENT

Fasting cortisol level was measured after 8-10hours of fasting.

Normal fasting cortisol – 5-25 microgram/dl

SEX DISTRIBUTION

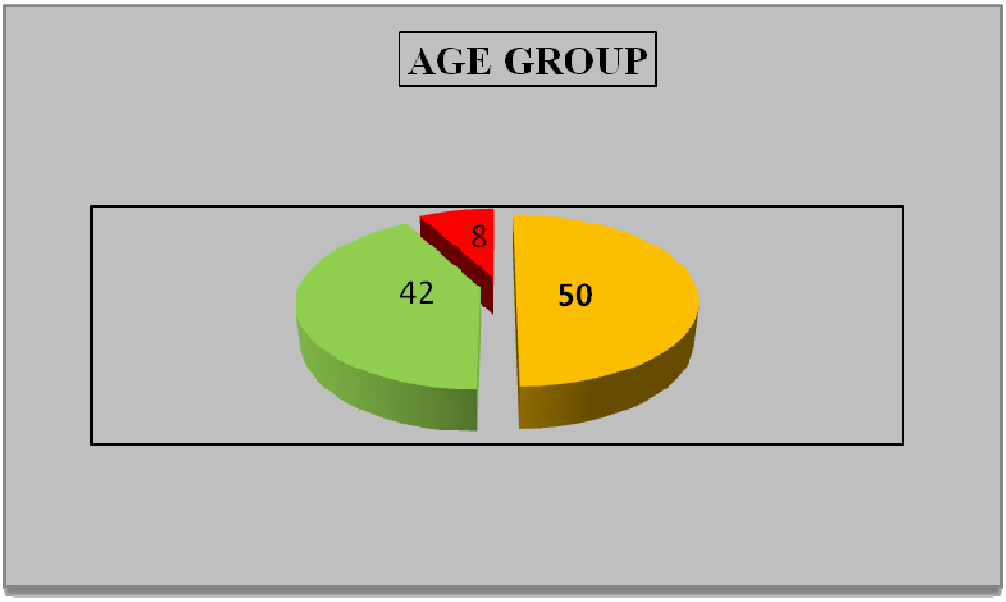


MALE: 52%

FEMALE: 48%

Out of 50 patients of type 2 diabets was studied 48% was females and 52% was males.

AGE DISTRIBUTION



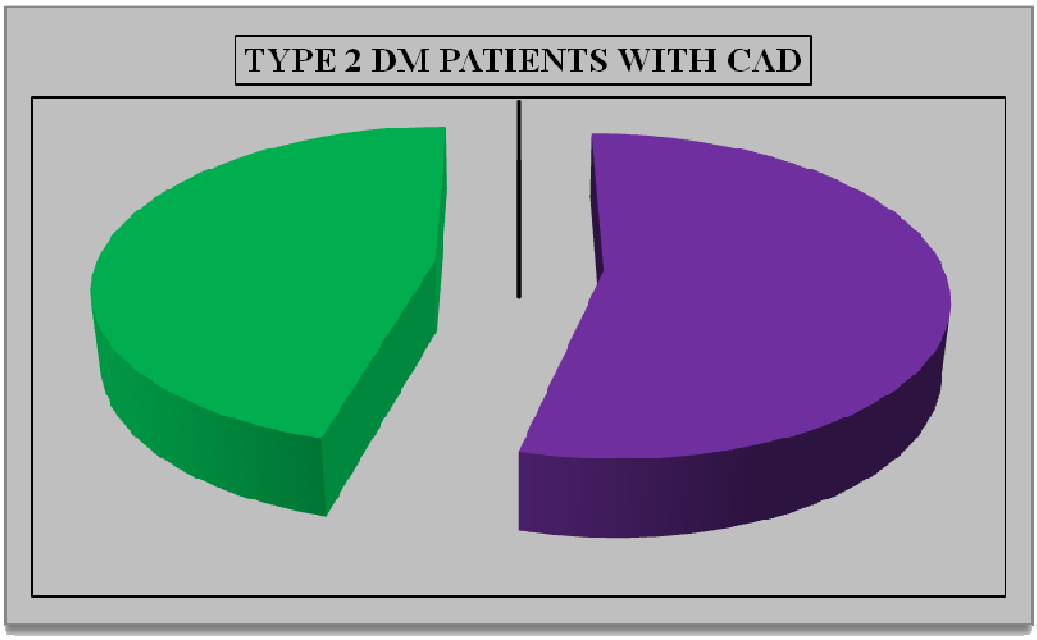
50-60 YEARS : **50%**

60-70 YEARS : **42%**

>70 YEARS : **8%**

Out of 50 patients of type 2 DM studied 50% was in the age group of 50-60 years, 42% was in between 60-70% and only 8% patients contributes > 70 years

TYPE 2 DM PATIENTS WITH CAD

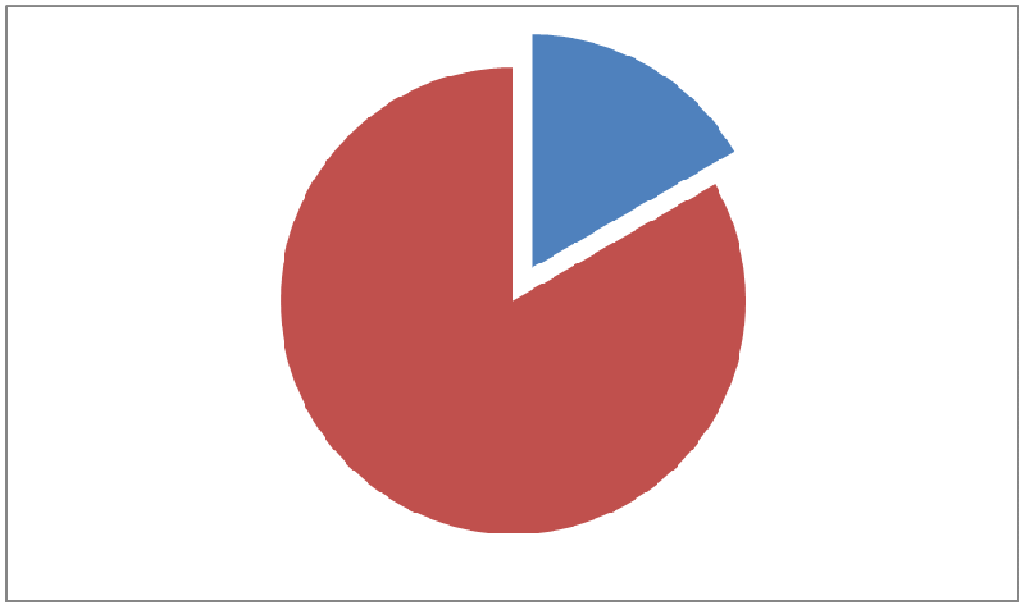


without CAD **54%**

with CAD **46%**

Out of 50 of type 2 DM patients 54% was without coronary artery disease and 46% patients was associated with CAD.

CORTISOL DISTRIBUTION IN TYPE 2 DM



ELEVATED CORTISOL 20%

NORMAL CORTISOL 80%

Out of 50 type 2 DM patients studied, 10 showed elevated fasting cortisol level; rest were normal.

AGE AND CORTISOL

Crosstab

			Fasting Cortisol		
			Normal	Elevated	Total
Age	Less than 60 years	Count	21	4	25
		% within Age	84.0%	16.0%	100.0%
		% within Fasting Corti	52.5%	40.0%	50.0%
	Between 60 - 70 ye	Count	16	5	21
		% within Age	76.2%	23.8%	100.0%
		% within Fasting Corti	40.0%	50.0%	42.0%
	Above 70 years	Count	3	1	4
		% within Age	75.0%	25.0%	100.0%
		% within Fasting Corti	7.5%	10.0%	8.0%
Total		Count	40	10	50
		% within Age	80.0%	20.0%	100.0%
		% within Fasting Corti	100.0%	100.0%	100.0%

In above table P value is .77 so > more than .05, it shows that there is no association between age and elevated cortisol.

Fasting Cortisol * CAD Crosstabulation

			CAD		
			Absent	Present	Total
Fasting Corti	Normal	Count	25	15	40
		% within Fasting C	62.5%	37.5%	100.0%
		% within CAD	92.6%	65.2%	80.0%
	Elevate	Count	2	8	10
		% within Fasting C	20.0%	80.0%	100.0%
		% within CAD	7.4%	34.8%	20.0%
Total		Count	27	23	50
		% within Fasting C	54.0%	46.0%	100.0%
		% within CAD	100.0%	100.0%	100.0%

In an attempt to study the association of cortisol level and coronary artery disease, out of 50 patients studied, 10 patients showed elevated cortisol, 40 patients had normal cortisol level. Out of 50 patients studied,23 had coronary artery disease. Among 10 patients with elevated cortisol,8 were associated with coronary artery disease.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Squar	5.817[b]	1	.016		
Continuity Correcti[a]	4.232	1	.040		
Likelihood Ratio	6.061	1	.014		
Fisher's Exact Tes				.030	.019
Linear-by-Linear Association	5.701	1	.017		
N of Valid Cases	50				

a. Computed only for a 2x2 table

b. 1 cells (25.0%) have expected count less than 5. The minimum expecte 60.

From the above table it can be concluded that the association between elevated fasting cortisol level and coronary artery disease is significant (p value < 0.05).

It means that in patients with elevated fasting cortisol level, there is an increased chance of coronary artery disease.

Discussion

DISCUSSION

An attempt has been made to study fifty cases of type 2 diabetes mellitus to study the association of cortisol level and coronary artery disease. In the cohort of 50 diabetic patients 23 had coronary artery disease, which comes to 46% of total patients. In the 50 type 2 diabetic patients, 22% had acute coronary syndrome; 24% had ischemic heart disease.

The Framingham Heart study revealed a marked increase in congestive heart failure, coronary artery disease and sudden cardiac death in type 2 diabetes mellitus patients(The risk increases from one to five fold in DM).The American Heart association has designated DM as a major risk factor for cardiovascular disease[(2)].

Among 50 DM patients, 52% were males and 48% were females. According to the Centre for Disease Control and Prevention (CDC), the prevalence of DM is similar in men and women throughout most age ranges but is slightly greater in men more than 60 years[(2)].

Conventional risk factors for coronary artery disease are diabetes mellitus, systemic hypertension, dyslipedemia, etc. Diabetes mellitus is the major risk factor for coronary artery disease. Newly proposed theory

is that there is an overactivity of hypothalamopituitary adrenal axis and elevated cortisol level[19].

Elevated cortisol is a single risk factor for coronary artery disease. According to Edinburg type 2 diabetes study, type 2 diabetic patients have hyperactive hypothalamopituitary adrenal axis and have elevated cortisol level and it was concluded that there is an increased chance of metabolic syndrome and coronary artery disease in patients with elevated cortisol level.

Out of 50 diabetic patients, 10 patients had elevated cortisol level.8 out of 10 patients with elevated level had coronary artery disease. This shows that there is an association between elevated cortisol level and coronary artery disease[19].

In our population, cortisol is only moderately elevated. Also, cortisol is elevated in patients who are having more than one complication of diabetes like dyslipedemia, central obesity, proteinuria and hypertension. Also, there is an association between elevated cortisol and coronary artery disease.

Conclusions

CONCLUSION

- There is hyperactivity of hypothalamopituitary axis in type 2 DM patients. Out of 50 patients,10 had mild to moderate elevation of fasting serum Cortisol.

- There is an association of elevated cortisol and high prevalence of coronary artery disease in patients with type 2 DM.

- Further studies are needed to find out the mechanism of hypothalamopituitary axis overactivity.

- Further studies are needed to find out the pathogenesis behind elevated cortisol causing coronary artery disease.

Annexures

Bibliography

BIBLIOGRAPHY

1. Davidsons principles and practice of medicine; (21st edition) cardiovascular disease . P. Bloomfield, abadbury , n.r grub
2. Harrisons principles of internal medicine; (17th edition) metabolic syndrome (robert h eikel); ischemic heart disease (riliot m antman, andrew p selwyn, eugene braunwald, joseph loscalzo)
3. Joslins diabetes mellitus (14th edition), definition ,diagnosis and classification of diabetes mellitus and glucose homeostasis. (peter h bennet, william c knowler)
4. Joslins diabetes mellitus, epidemiology of dm (james h warren , antazej s krolewski) insulin resistance and its role in the pathogenesis of type 2 dm;(meredith hawkins and luciano rosseti)
5. Joslins diabetes mellitus mechanism of diabetic microvascular complications (christian rask-madson , zhileng he ,and george king)
6. Joslins diabetes mellitus pathogenesis of cardio vascular disease in diabetes (edward p feener and victor p feener)
7. Williams text book of endocrinology (11th edition) the adrenal cortex;

   (paul m stewart)

8. Williams text book of endocrinology; complications of diabetes mellitus (michael brown lee; loyd p aiello,mark e cooper)
9. Braunwald et al
10. cortisol secretion in patients with type 2 diabetes relationship with chronic complications
11. Iacopo chiodini, md1, guido adda, md2, alfredo scillitani, md3, francesca coletti, md2, valentina morelli, md2, sergio di lembo, md2, paolo epaminonda, md2, benedetta masserini, md2, paolo beck-peccoz1, emanuela orsi, md1, bruno ambrosi4 and maura arosio12
12. andrews rc, herlihy o, livingstone de, andrew r, walker br: abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance. J clin endocrinol metab 87:5587–5593, 2002
13. arnaldi g, angeli a, atkinson ab, bertagna x, cavagnini f, chrousos gp, fava ga, findling jw, gaillard rc, grossman ab, kola b, lacroix a, mancini t, mantero f, newell-price j, nieman lk, sonino n, vance ml, giustina a, boscaro m: diagnosis and complications of cushing's syndrome: a consensus statement. J clin endocrinol metab 88:5593
14. tauchmanovà l, rossi r, biondi b, pulcrano m, nuzzo v, palmieri ea, fazio s, lombardi g: patients with subclinical cushing's sindrome

have increased cardiovascular risk. J clin endocrinol metab 87:4869–4871, 20

15. (circulation. 2005;112:332-340.)

Cortisol, testosterone, and coronary heart disease

Prospective evidence from the caerphilly study

George davey smith, dsc; yoav ben-shlomo, bsc, mbbs, mrcp, ffphm, phd; andrew beswick, bsc; john yarnell, mbchb, dph, mscm, md, mfphm (ire), ffphm; stafford lightman, mbchb, phd, fmedsci; peter elwood, dsc, md, frcp, ffphm

16. Macleod j, davey smith g, heslop p, metcalfe c, carroll d, hart c. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study on scottish men. Bmj. 2002; 324: 1247–1251.

17. the journal of clinical endocrinology & metabolism vol. 83, no. 3 757-760

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Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome

D. I. W. Phillips, d. J. P. Barker, c. H. D. Fall, j. R. Seckl, c. B. Whorwood, p. J. Wood and b. R. Walker

18. circulating plasma cortisol concentrations are not associated with coronary artery disease or peripheral vascular disease

r.m. Reynolds[1], b. Ilyas[1], j.f. Price[2], f.g.r. Fowkes[2], d.e. Newby[1], d.j. Webb[1] and b.r. Walker[1]

19. the journal of clinical endocrinology & metabolism vol. 95, no. 4 1602-1608 copyright © 2010 by the endocrine society

Elevated fasting plasma cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: the edinburgh type 2 diabetes study

Rebecca m. Reynolds, javier labad, mark w. J. Strachan, anke braun, f. Gerry r. Fowkes, amanda j. Lee, brian m. Frier, jonathan r. Seckl, brian r. Walker, jackie f. Price on behalf of the edinburgh type 2 diabetes study (et2ds) investigators

PROFORMA

STUDY TO ANALYZE THE ASSOCIATION OF CORTISOL LEVEL AND CORONARY ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

NAME: **AGE:** **SEX:**

ADDRESS:

SYMPTOM	SIGN
POLYURIA	PEDAL OEDEMA
POLYDYPSIA	PULSE
POLYPHAGIA	BP
CHEST PAIN	
EXERTIONAL BREATHLESSNESS	

PULSE	
BP	
WC	
HT	
WT	

CVS	
RS	
CNS	
ABD	

INVESTIGATIONS	
RBS	
FBS	
PPBS	
FASTING LIPD PROFILE	
FASTING CORTISOL	

ECHO	
ECG	

S.NO.	AGE	SEX	PR	BP	WC	RBS	FBS	PPBS	LDL	F.CORT	UR.PROT	ECG	ECHO
1	57	M	74	114/82	86	240	138	238	152	11 N	-	NORMAL	NO RWMA , EF NORMAL
2	59	M	80	170/110	82	223	182	257	247	34 ↑	2+	IWMI	hypokinesia of inferior wall,EF normal
3	66	F	84	150/90	84	196	146	240	198	8 N	-	NORMAL	NO RWMA,EF normal
4	69	M	88	110/90	91	250	184	240	138	18 N	-	NORMAL	NO RWMA,EF normal
5	59	M	76	158/94	109	204	146	280	178	12 N	-	AW ischemia,	NO RWMA,EF normal
6	66	M	80	126/74	100	230	200	294	130	14 N	-	NORMAL	NO RWMA,EF normal
7	67	M	78	164/90	96	217	170	248	240	14 N	-	NORMAL	NO RWMA,EF normal
8	60	F	82	160/90	86	188	152	206	158	11 N	-	NORMAL	NO RWMA,EF normal
9	54	M	70	170/94	104	212	162	270	186	4.5 N	-	IW ischemia	NO RWMA,EF normal
10	70	F	88	170/100	96	204	162	224	200	10 N	-	IW ischemia	NO RWMA,EF normal
11	70	M	76	114/66	88	224	180	300	155	13 N	-	NORMAL	NO RWMA,EF normal
12	61	F	70	166/80	83	208	168	280	175	15 N	-	AW ischemia,	NO RWMA,EF normal
13	69	F	90	180/110	90	250	168	240	174	5 N	-	Lateral wall ischemia	NO RWMA,EF normal
14	64	M	84	110/70	90	216	174	298	160	20 N	-	NORMAL	NO RWMA,EF normal
15	64	F	86	178/98	86	270	200	360	210	21 N	-	IW ischemia	NO RWMA,EF normal
16	53	M	72	190/100	97	208	140	226	210	19 N	1+	ASMI	Hypokinesia of anterior wall ,EF42%
17	62	M	92	128/74	88	174	144	268	148	8 N	-	NORMAL	NO RWMA,EF normal
18	62	F	82	120/80	82	180	150	240	140	10 N	-	NORMAL	NO RWMA,EF normal
19	70	F	70	180/100	98	233	197	306	216	35 ↑	2+	HLMI	Hypokinesia of lateral wall, EF normal
20	59	F	82	142/90	92	200	138	214	137	20 N	-	NORMAL	NO RWMA,EF normal
21	51	F	66	136/82	97	193	143	238	159	8 N	-	NORMAL	NO RWMA,EF normal
22	67	F	64	180/106	108	263	189	303	217	38↑	1+	IWMI	Hypokinesia of inferior wall EF normal mild mr
23	64	M	70	150/90	94	198	220	290	175	36 ↑		IWMI	hypokinesia of inferior wall EF normal mild mr
24	59	M	74	110/70	94	164	138	240	154	7.2 N	-	NORMAL	NO RWMA,EF normal
25	54	F	82	110/76	92	200	140	218	153	15 N	-	NORMAL	NO RWMA,EF normal
26	61	M	84	180/94	104	215	166	250	219	20 N	-	AW ischemia	NO RWMA,EF normal
27	58	F	86	100/70	93	178	130	266	136	9.5 N	-	NORMAL	NO RWMA,EF normal
28	58	F	74	100/70	90	196	138	210	147	9 N	-	NORMAL	NO RWMA,EF normal
29	55	M	70	140/98	106	225	302	380	230	38 ↑	2+	EXTENSIVE AW MI	Hypokinesia of AW,EF 35%, dilated LV
30	54	M	78	160/92	98	216	150	280	170	30 ↑	-	NORMAL	NO RWMA,EF normal
31	77	F	76	168/88	88	219	168	272	180	12 N	-	AW Ischemia	NO RWMA,EF normal
32	71	M	82	160/90	96	218	178	248	250	28 ↑	-	NORMAL	NO RWMA,EF normal
33	58	M	80	150/90	112	265	164	288	256	32 ↑	2+	ASMI	Hypokinesia o Aw, EF35% cardiac chambers dilated
34	68	M	68	100/80	96	192	172	288	142	6 N	-	NORMAL	NO RWMA,EF normal
35	73	F	76	160/98	92	240	180	289	218	22 N	-	IW ischemia	NO RWMA,EF normal
36	59	M	92	184/90	106	210	150	238	224	12 N	1+	IL ischemia	NO RWMA,EF normal
37	75	F	84	154/90	80	190	133	226	140	22 N	-	NORMAL	NO RWMA,EF normal
38	80	F	86	140/90	104	207	138	280	139	13 N	-	NORMAL	NO RWMA,EF normal
39	52	M	90	160/92	106	228	140	225	200	32 ↑	2+	IWMI	NO RWMA,EF normal
40	68	F	88	150/88	90	198	144	230	133	18 N	-	NORMAL	NO RWMA,EF normal
41	77	F	80	138/88	100	203	152	250	143	7 N	-	NORMAL	NO RWMA,EF normal
42	58	M	76	168/88	108	221	170	263	230	17 N	-	AWMI	hypokinesia of AW, EF normal
43	50	M	90	140/100	107	216	150	258	146	16 N	-	AWMI	hypokinesia of AW, EF normal
44	69	F	64	130/84	82	183	150	242	151	24 N	-	NORMAL	NO RWMA,EF normal
45	62	F	68	112/80	94	187	127	206	160	5 N	-	NORMAL	NO RWMA,EF normal
46	67	F	76	180/100	82	216	162	280	146	8 N	-	AW ischemia	NO RWMA,EF normal
47	68	F	72	160/94	92	220	160	284	150	5 N	-	AS ischemia	NO RWMA,EF normal
48	63	M	78	120/80	96	196	165	280	140	14 N	-	NORMAL	NO RWMA,EF normal
49	60	F	64	118/76	88	192	142	223	150	12 N	-	NORMAL	NO RWMA,EF normal
50	63	F	86	170/96	100	240	170	298	243	37 ↑	2+	ASMI	Hypokinesia of anterior wall, EF46%, cardiac chambers dilated

ABBREVIATIONS

ACTH	Adreno Corticotropic Hormone
AGE	Advanced Glycation Endproducts
ASMI	Anteroseptal Myocardial Infarction
ATP	Adult Treatment Panel
AVP	Arginin Vasopressin
AWMI	Anterior Wall Myocardial Infarction
BP	Blood Pressure
CAD	Coronary artery Disease
DM	Diabetes Mellitus
ECM	Extra Cellular Matrix
EF	Ejection Fraction
FBS	Fasting Blood Sugar
HDL	High Density Lipo Protein
HLMI	High Lateral Wall Myocardial Infarction
HPAA	Hypothalamo Pituitary Adrenal Axis
IL	Interleukin
MMP	Matrix Metallo Proteinase
PR	Pulse Rate
PPBS	Post Prandial Blood Sugar
RBS	Random Blood Sugar
RWMA	Regional Wall Motion Abnormality
SHT / SHTN	Systemic Hypertension
WC	Waist Circumference

CONSENT FORM

Yourself Mr/Mrs/Ms _____ are being asked to be a participant in the study titled – **STUDY TO ANALYZE THE ASSOCIATION OF CORTISOL LEVEL AND PREVALENCE OF CORONARY ARTERY DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS** by Dr Aryamol M.K, Post Graduate student, Department of General Medicine,Coimbatore Medical College. You are eligible after looking into inclusion criteria. You can ask any questions you may have before agreeing to participate.

Purpose of the research

To analyze the association of cortisol level and prevalence of coronary artery disease in patients with type 2 diabetes mellitus

Procedures involved

This research is intended to study type 2 daiabetes mellitus patients and to analyse the association of cortisol level and prevalence of coronary disease in these patients.

Decline from participation

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

Privacy and confidentiality

Privacy of individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization publish results

Results of the study may be published for scientific purposes and / or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me and I may ask questions at any time.

_____ _____

Signature of Left Hand thumb Impression Date

(Volunteer Subject)

_____ _____

Signature (Witness) Date