A dissertation on

A CASE CONTROL STUDY ON THE RELATIONSHIP BETWEEN SERUM FERRITIN LEVELS AND TYPE 2 DIABETES MELLITUS AND ITS PROSPECTS AS A DIABETES CONTROL INDEX

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CERTIFICATE

This is to certify that the dissertation entitled **"A CASE CONTROL STUDY ON THE RELATIONSHIP BETWEEN SERUM FERRITIN AND TYPE 2 DIABETES MELLITUS AND ITS PROSPECTS AS A DIABETES CONTROL INDEX"** is a bonafide work done by **Dr. S.SRIVIDHYA,** at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under our guidance and supervision during the academic year 2017-2020.

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LIST OF ABBREVIATIONS

DM	-	Diabetes mellitus
TCF7L2	-	Transcription factor 7 like 2
SLC30A8	-	Solute carrier family 30 member 8
GWAS	-	Genome wide association studies
IL-6	-	Interleukin 6
IL-8	-	Interleukin 8
G-CSF	-	Granulocyte colony stimulating factor
IL-1	-	Interleukin 1
NAD	-	Nicotinamide adenine dinucleotide
NEAT	-	Non exercise activity thermogenesis
TGF-beta	-	Transforming growth factor beta
GLUT4	-	Glucose transporter type 4
PCOS	-	Polycystic ovarian syndrome
GLP1-RA	-	Glucagon like peptide 1 receptor agonist
PPAR	-	Peroxisome proliferator activated receptor
DPP	-	Dipeptidyl peptidase
ADA	-	American diabetes association

CONTENTS

S. NO.	TITLE	PAGE NO.
1	INTRODUCTION	1
2	AIMS AND OBJECTIVES	4
3	REVIEW OF LITERATURE	6
4	MATERIALS AND METHODS	54
5	OBSERVATION AND RESULTS	57
6	DISCUSSION	79
7	CONCLUSION	85
8	LIMITATION OF STUDY	87
9	BIBLIOGRAPHY	89
10	ANNEXURES	95
	- PROFORMA - ETHICAL COMMITTEE APPROVAL - PLAGIARISM SCREENSHOT - PLAGIARISM CERTIFICATE - INFORMATION SHEET - CONSENT FORM - MASTER CHART	

INTRODUCTION

INTRODUCTION

Diabetes mellitus is a metabolic disorder that mainly portrays the phenotype of hyperglycemia. The various types of diabetes mellitus are the result of a complex interaction between genes and environmental factors. The two major categories of diabetes are type 1 and type 2 though other forms have also been increasingly recognized. A complete or near total insulin deficiency defines type 1 diabetes whereas type 2 is characterized by insulin resistance in variable grades.

Of the two, our topic of interest remains to be type 2 diabetes mellitus and the disease by itself is polygenic and multifactorial. Its etiopathogenesis is still an unresolved mystery and various factors such as impaired insulin secretion, insulin resistance, excessive hepatic glucose production, abnormal fat metabolism and low grade systemic inflammation are said to contribute.

Monitoring the level of blood sugars includes plasma glucose level measurements as well as a long term assessment marker such as HbA1c, keeping in mind that both these measurements are actually complementary to each other. The need for a marker of diabetes control has still been unmet with an ideal marker not requiring fasting but still cost affordable.

Ferritin on the other hand is the storage form of iron and is also an acute phase reactant. It is a globular protein complex containing 24 protein subunits giving rise to a nanocage with lots of metal-protein interactions. Ferritin also has other important roles to play such as protecting the body from oxidative damage.

Since in diabetes, there is believed to be a low grade of systemic inflammation serum ferritin levels could very well be a marker for the activity of the disease in affected individuals. Moreover the iron status plays a major role in regulating insulin resistance.

Thereby, estimating the levels of serum ferritin in type 2 diabetes patients without any acute infection will lead us to the luxury of having another marker for diabetes control and possible insight into the pathogenesis of diabetes.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To determine the relationship between type 2 diabetes mellitus and serum ferritin

- To explore the prospects of serum ferritin as a marker for diabetes control

REVIEW OF LITERATURE

REVIEW OF LITERATURE

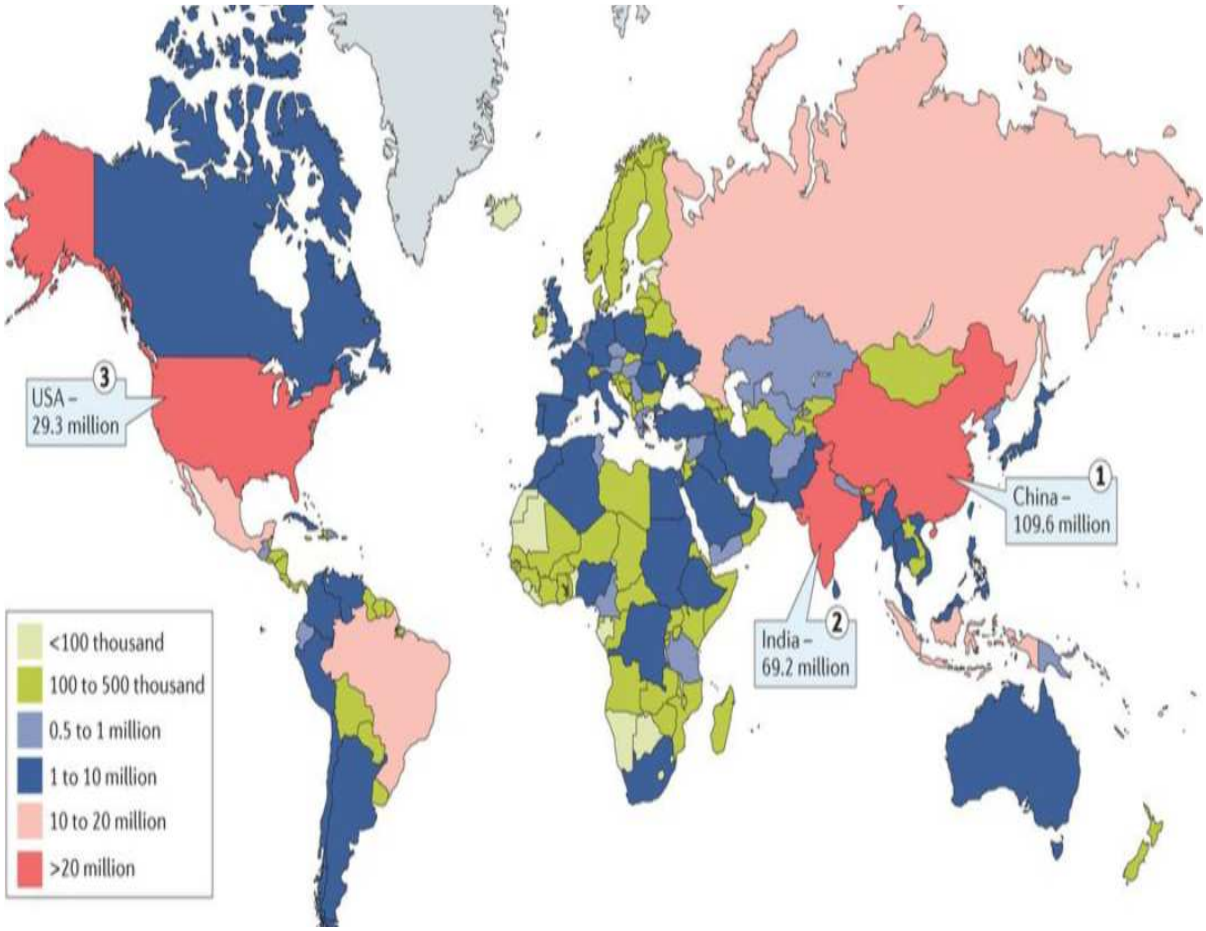
Diabetes mellitus is a complex metabolic disorder that features hyperglycemia which either results from defective insulin secretion or resistance to the action of insulin or sometimes, even both. It is classified into four main types that include type 1, type 2, gestational and other types of diabetes mellitus. Now, type 1 diabetes mellitus is predominantly caused due to autoimmune destruction of the insulin secreting beta cells of the pancreas. Type 2 diabetes mellitus on the other hand, is the hero of our study and is also the most common type of diabetes.

EPIDEMIOLOGY

The number of people with diabetes mellitus has increased fourfold times over the past 30 years. 90% of all individuals with diabetes have type 2 diabetes mellitus only. Even though genetic predisposition plays a major role in deciding who becomes a diabetic, an unhealthy lifestyle is also an equally important contributing factor. Most cases are diagnosed after 40 years of age. This approximates to a lifetime risk of developing diabetes of 1in 10.

Regional differences in the prevalence of diabetes may be attributed to the different environments and also their own genetic susceptibility. The crude prevalence rate of diabetes in India is thought to be around 9%. Considering the huge population of our nation, this may reflect our burden of diabetes. Also, impaired glucose tolerance is an emerging problem in India. The prevalence of

impaired glucose tolerance in India is estimated to be at 8.7%. Nearly 35% of this population who have impaired glucose tolerance will proceed to develop florid diabetes mellitus. Truthfully, it would be an understatement to say that India is currently facing nothing short of a health care crisis.



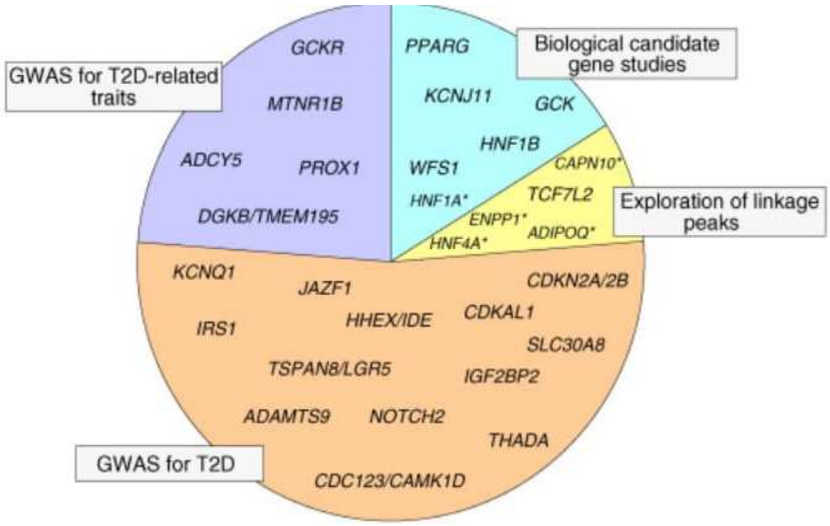
ETIOPATHOGENESIS

The major risk factors for diabetes may be classified as environmental and unmodifiable. The heritability for type 2 diabetes is greater than that for Type 1 and can therefore account for up to 40-80% of disease susceptibility. Similarly, maternal diabetes has a higher chance of manifesting in the offspring rather than

paternal diabetes. In recent years, there has been a lot of research in the genetics of type 2 diabetes mellitus. Previous genetic studies used either candidate gene approach which was based on the knowledge of pathways involved in glucose regulation or, linkage studies. Though both these approaches have helped in the identification of a significant number of genes, it is in fact the application of Genome wide association studies that has resulted in the discovery of a great number of diabetes related genes. The first GWAS for type 2 DM showed the TCF7L2 gene association and SLC30A8 which encodes a zinc transporter expressed in beta cells.

Based on various such genetic studies, the following conclusions can be drawn:

- The genes discovered till date account only for a small proportion of the population at risk.
- When there are many at risk polymorphisms in a single person there is a much higher risk of developing diabetes.
- A large number of the genes identified so far appear to increase the risk for diabetes by decreasing insulin secretion rather than increase insulin resistance.
- This may cause a slight confusion in the roles of both these factors mentioned above.

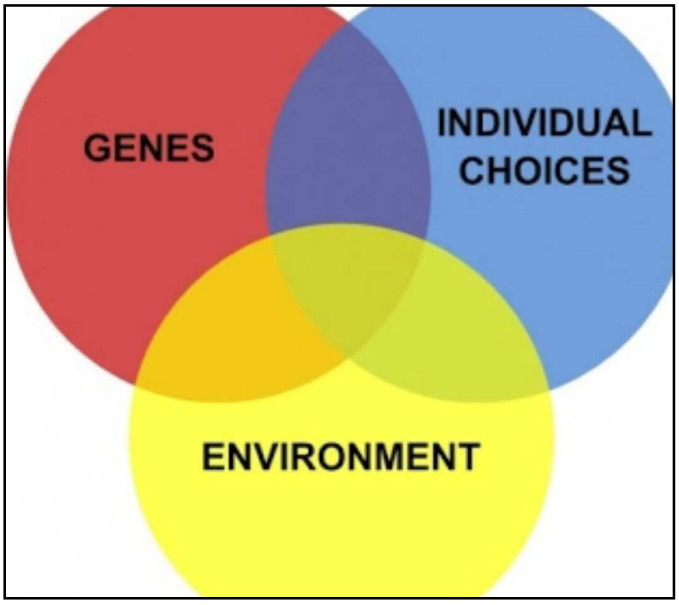


INSULIN RESISTANCE

The term insulin resistance refers to a subnormal biological response to insulin that is either secreted endogenously or given exogenously. Insulin sensitivity depends upon a number of factors such as age, weight, abdominal fat, physical exercise and medications as well. First degree relatives of type 2 DM patients will have insulin resistance even before they become obese, indicating that there is a stronger genetic component in the development of diabetes.

The absolute amount of body fat present in an individual plays an important role in determining the insulin sensitivity. However central obesity has a greater association with insulin resistance and also a number of other parameters such as, plasma glucose, and total plasma cholesterol and triglyceride concentrations. The reason for this could be that abdominal fat undergoes more lipolysis when compared to subcutaneous fat as it has a higher number of adrenergic receptors. The abdominal fat is also more resistant to the lipolytic

action of insulin and so a higher proportion of fatty acids are released into the circulation. Of this, the portal circulation receives the highest fatty acid load. Abdominal fat has high levels of 11 beta hydroxyl steroid dehydrogenase which converts cortisone to cortisol. Increased amounts of local cortisol will alter adipokines production and thereby increase lipolysis.



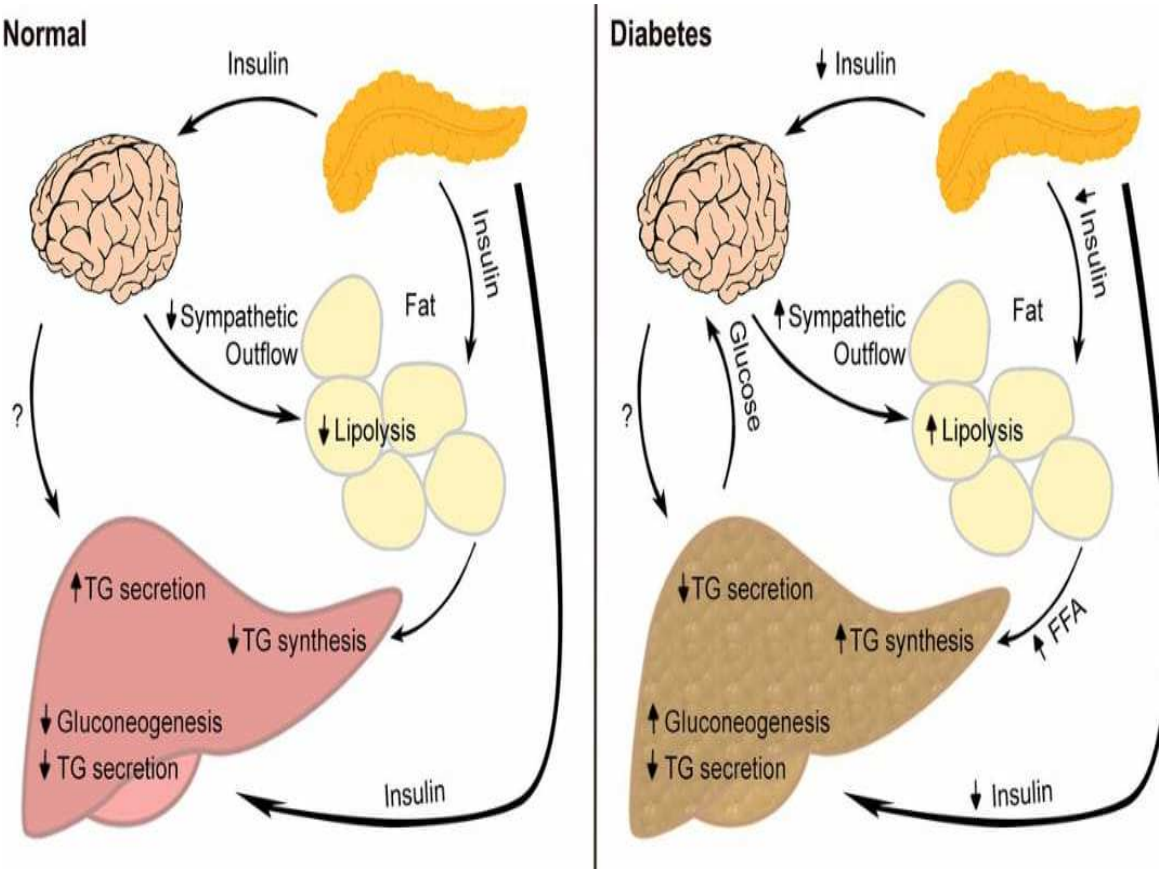
A number of interacting factors in between the tissues will decide the phenotypic response of an individual to nutrient overload. For maintaining metabolic homeostasis excess nutrients must be stored as fatty acids in the form of triglycerides. These stored nutrients can be mobilized when an energy deficit occurs. But if the storage capacity of adipose tissue is exceeded, then fats also tend to enter non adipose tissues such as muscle cells, hepatocytes, endothelial cells and even beta cells. When the adipocyte surface area increases, as in obesity, there is also an increase in the expression of substances such as leptin, IL-6, IL-8

and G-CSF. The expression of these substances attracts macrophages and once the macrophages arrive, there is a swirl of systemic inflammation.

In obesity, there is activation of an unfolded protein response. This response is seen in many organs including the liver, adipose tissue and pancreas. It causes the activation of pathways such as Janus Kinase pathways which lead to decreased insulin sensitivity.

Innate immunity can produce inflammasomes, which are protein complexes that control the post translational maturation of interleukins and also their secretion, mainly IL-1beta. As is evident, these can have potent proinflammatory responses and form some of the major risk factors for the development of type 2 DM. The stimulation of secretion of this cytokine may also damage or disrupt the beta cell functioning. Activation of Toll-like receptors in cells can lead to insulin resistance. In fact, the treatment of diabetics with anakinra, an IL-1 antagonist reduced plasma glucose values and increased insulin secretion, again emphasizing on the relationship between innate immune systems and the development of diabetes.

Insufficient sleep or poor quality sleep impairs the action of insulin and raises the levels of ghrelin n the blood, which stimulates appetite. Therefore the circadian rhythm is important in maintaining glucose homeostasis. Obesity related sleep apnoea itself can further exacerbate these effects. The treatment of this condition may improve the cognitive symptoms but an improvement in the metabolic changes is yet to be documented.



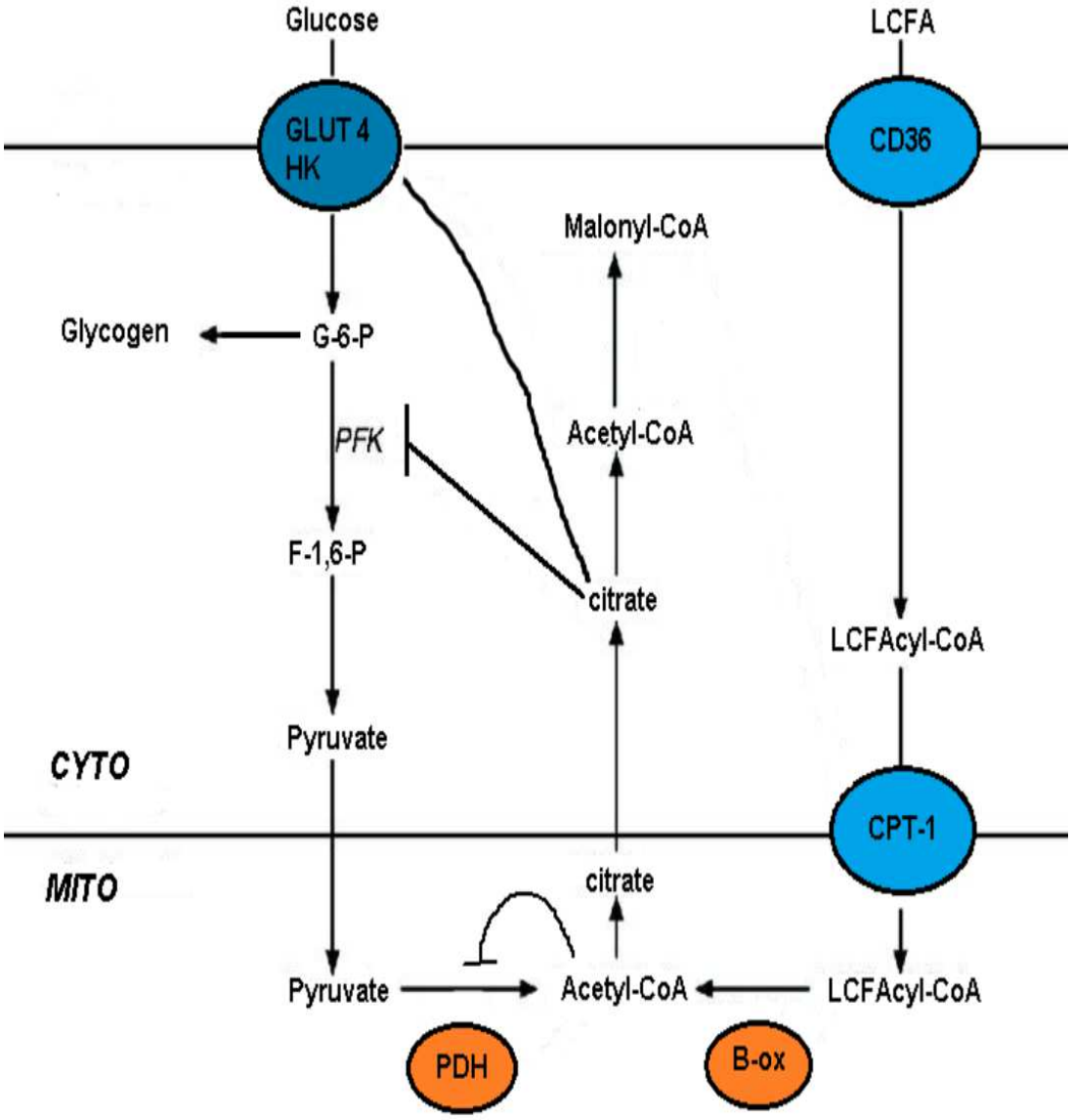
Once a meal is completed, the excess glucose is deposited in the skeletal muscles after its conversion to glycogen. But the skeletal muscles can only store so much and that is the reason why insulin resistance is appreciated earlier in the skeletal muscle even before in the liver or adipose tissue. Insulin resistance worsens the situation by causing a defect in glycogen synthesis. When the system of non oxidative glucose disposal is affected, diabetes mellitus sets in.

Increased free fatty acid levels enhance the chance of progression from impaired glucose tolerance to diabetes mellitus. Both the liver and skeletal muscles extract a sizeable amount of fatty acids from the periphery and hence the measurement of peripheral free fatty acids will not reflect the true burden. High

levels of fatty acids inhibit substrate oxidation of glucose in the muscle. It competes with glucose for oxidation and increases mitochondrial levels of acetyl coenzyme A. It also reduces levels of NADH/NAD+, with subsequent inhibition of pyruvate dehydrogenase. This results in the accumulation of citrate inside the cell which inhibits phosphofructokinase, the important rate controlling enzyme in glycolysis. So glucose 6 phosphate accumulates inside the cell, causing decreased glucose uptake. This phenomenon is known as the Randle hypothesis.

However in normal subjects raised levels of free fatty acids have not been found to increase intracellular glucose concentrations. In fact, there has been a fall in intracellular glucose concentrations which preceded the fall in glycogen accumulation. These results have been found to question the Randle hypothesis which states that free fatty acids increase intracellular glucose concentration.

Protein kinase C mediated serine phosphorylation of the Inhibitor of nuclear factor Kappa beta leads to unregulated translocation of nuclear factor Kappa beta into the nucleus and this mediates the insulin resistance associated with high levels of free fatty acids. This mechanism probably elucidates how aspirin may positively affect insulin resistance as high dose aspirin can cause disruption of the IKKbeta pathway.

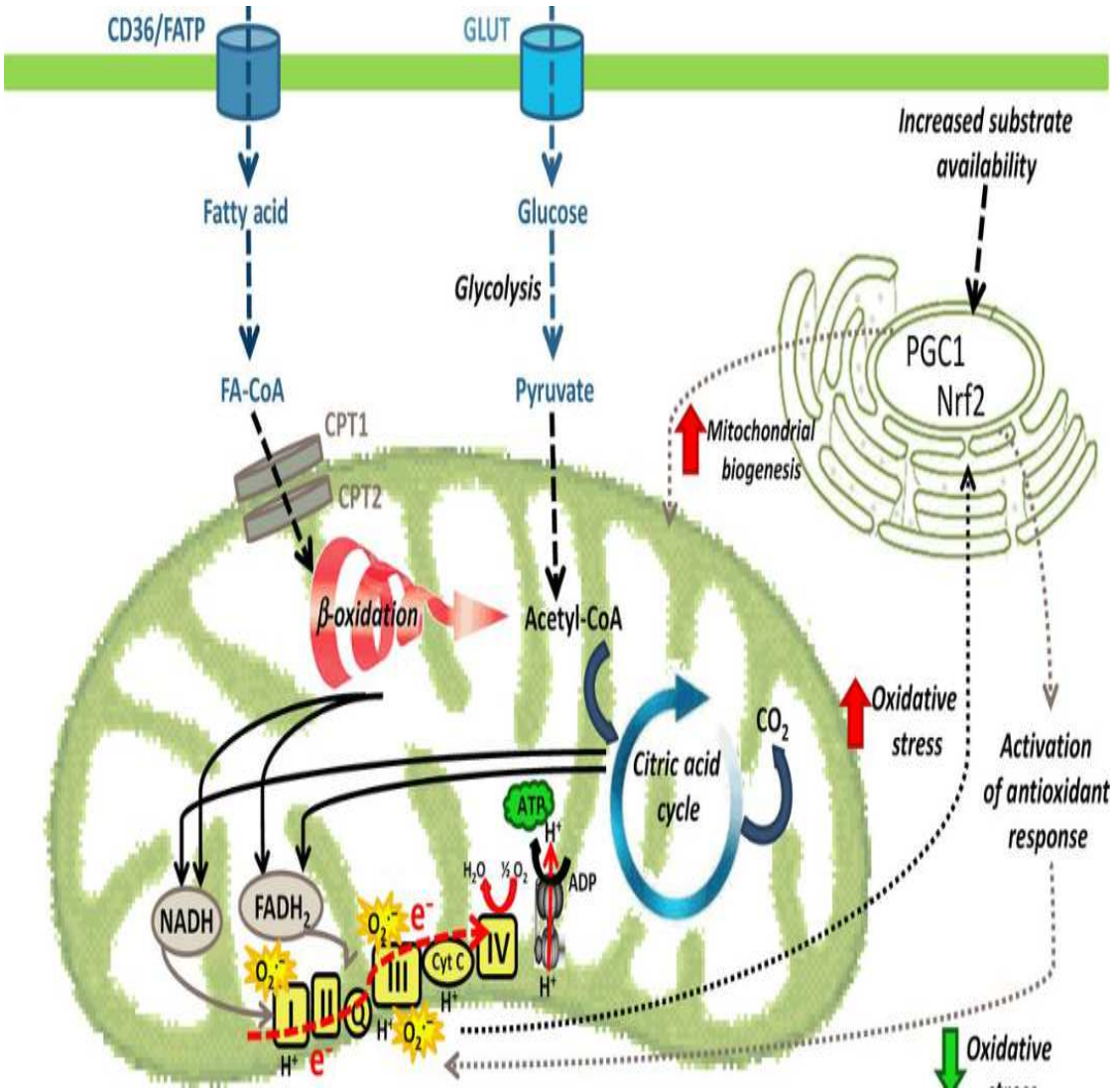


Insulin induced glucose uptake is also inversely proportional to the triglyceride content of the muscle. MRI can differentiate intracellular from extracellular fat in the muscles and highlight the triglyceride content in the myofiber. This theory of increased triglyceride content and insulin resistance cannot be generalized though as even exercise increases intramuscular triglyceride levels but also heightens insulin receptor sensitivity.

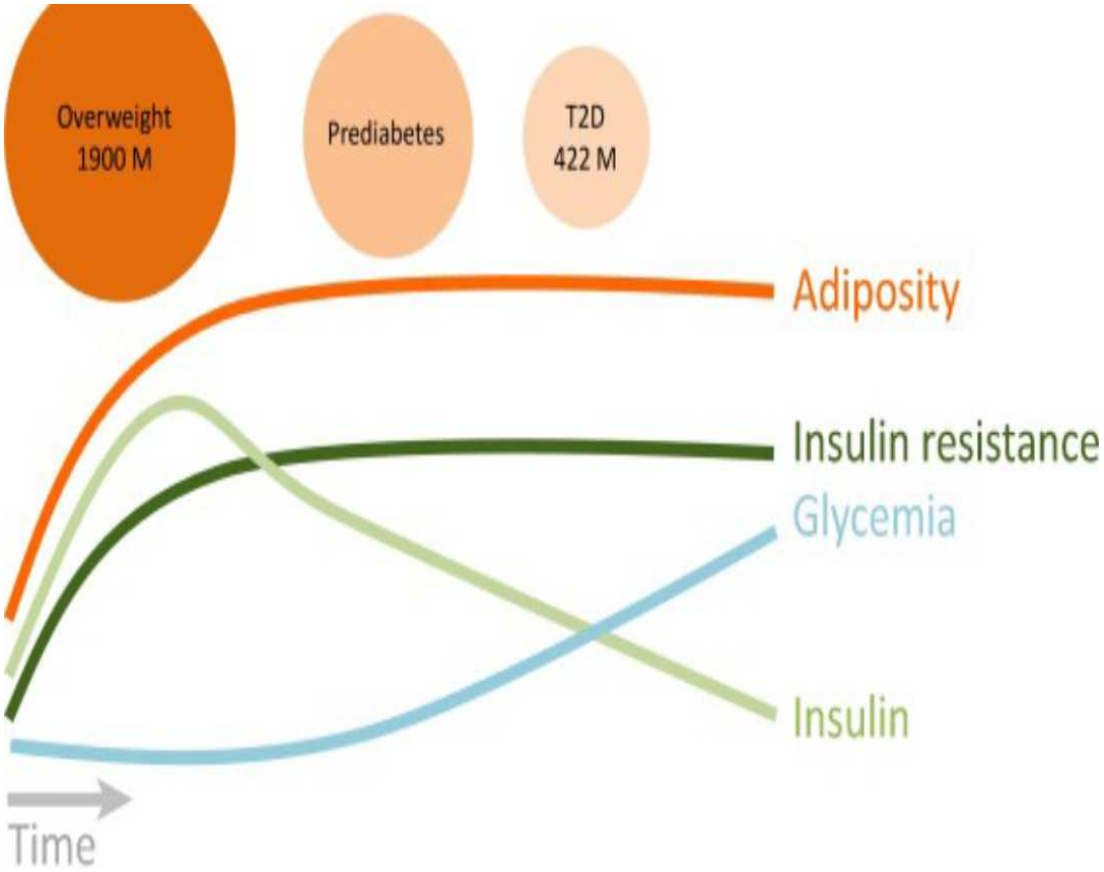
Insulin resistance is characterized by a decrease on oxidative capacity. The lipid content of the muscle cells is found to take a toll on the mitochondrial mass. This attributes to the reduction in mitochondrial oxidative capacity. The type 1 muscle fibers are generally more oxidative and contain a greater number of mitochondria when compared to type 2 fibers. The type 2 fibers are mainly glycolytic. The mitochondria inside the myofibrils are found to be smaller in the diabetic population and electron transport chain activity is also reduced. It has also been shown that the activity of the electron transport chain and the size of the mitochondria correlate with the severity of insulin resistance.

People with poor aerobic capacity or those who have never once practiced aerobic exercises in their lives are found to have a number of abnormalities including obesity, insulin resistance, and hypertension. The above mentioned facts could possibly suggest that the defects in metabolism have a stronger genetic basis.

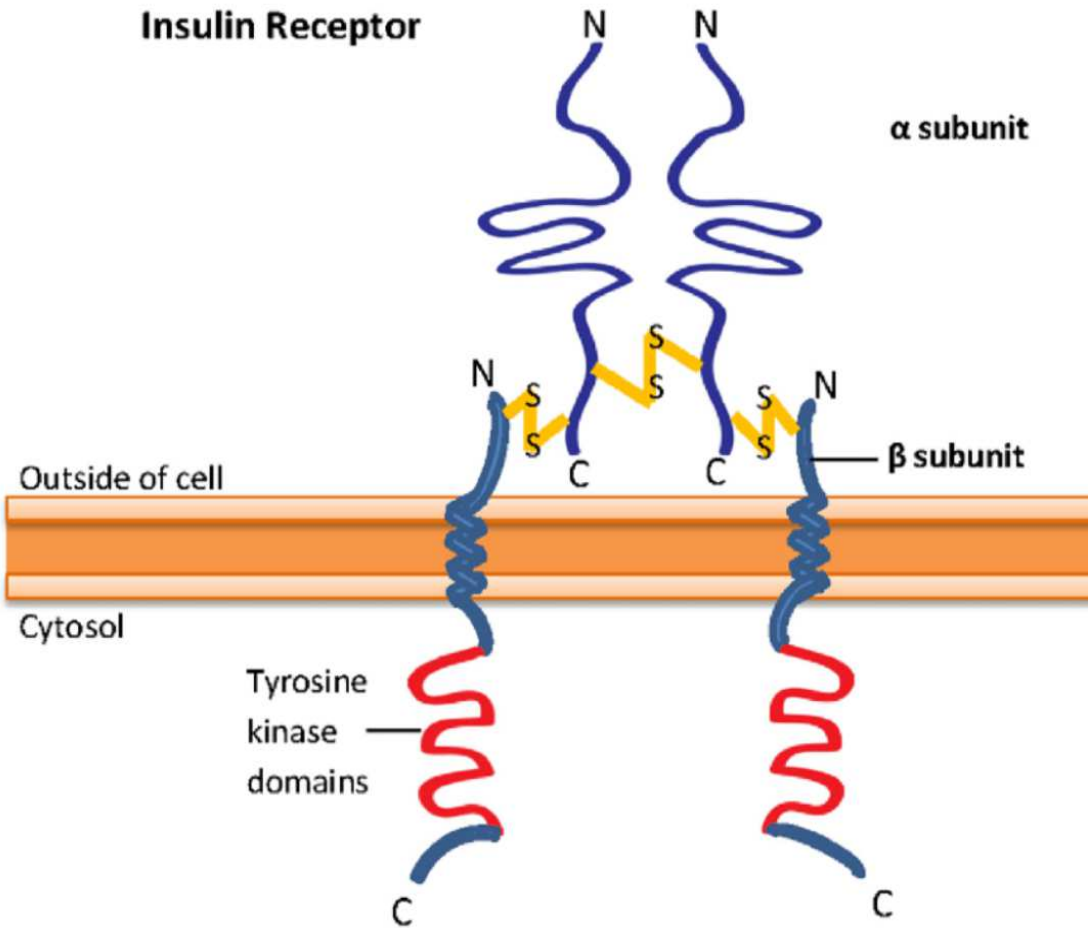
NEAT (non exercise activity thermogenesis), an emerging concept in the present is equal to the energy spent for everything that is not basal or exercise related. The slight differences in activity throughout the day can consume about 350 calories in one day. Long term differences in this energy expenditure could affect or cause changes in skeletal muscle metabolism. This is an active area of research at present.



Hyperinsulinemia y itself can cause insulin resistance. High concentrations of insulin can cause down regulation of the insulin receptors and desensitize the pathways. It has been shown that prolonged hyperinsulinemia (for more than 24 and 72 hours); even in normal individuals inhibits the insulin from causing non oxidative disposal of glucose. This is because of an impaired ability of the insulin to stimulate glycogen synthase. In obese and overweight persons, insulin levels can be brought down in order to increase the insulin sensitivity.



Insulin signaling affects many processes such as amino acid metabolism, protein synthesis and apoptosis. Insulin signaling is activated via cell surface receptor binding and a cascade of phosphorylation and dephosphorylation events occur in succession along with the generation of second messengers and also inter-protein interactions which result in a number of metabolic events in every tissue. The insulin receptor has two parts to it. Insulin itself binds to the alpha subunit which is extracellular and activates the intracellular portion or the beta subunit. The beta subunit is also liable to undergo serine or threonine phosphorylation. Any intervention that decreases the serine phosphorylation of the beta subunit of the insulin receptor actually increases insulin signaling.



Once the receptor is internalized and protein tyrosine phosphatases dephosphorylate it, insulin signaling stops.

Thereby increased activity of the above mentioned enzyme can also attenuate insulin signaling. Two protein tyrosine phosphatases PTP1B and LAR are increased in those with insulin resistance. Mutations which are associated with the number of insulin receptors, their splicing, trafficking, binding and phosphorylation can all cause forms of insulin resistance.

An excess amount of glucocorticoids have always been known to cause significant insulin resistance. Though the exact mechanism is not known, fat gets redistributed from the periphery to the central compartments of the body.

Glucocorticoids also raise the levels of free fatty acids and triglycerides in the blood. At a molecular level steroid also has its effects on the proteins which are necessary for the action of insulin in the liver and the muscles. Steroids can raise glucose concentrations and elevate blood pressures through the activation of PPARalpha receptors.

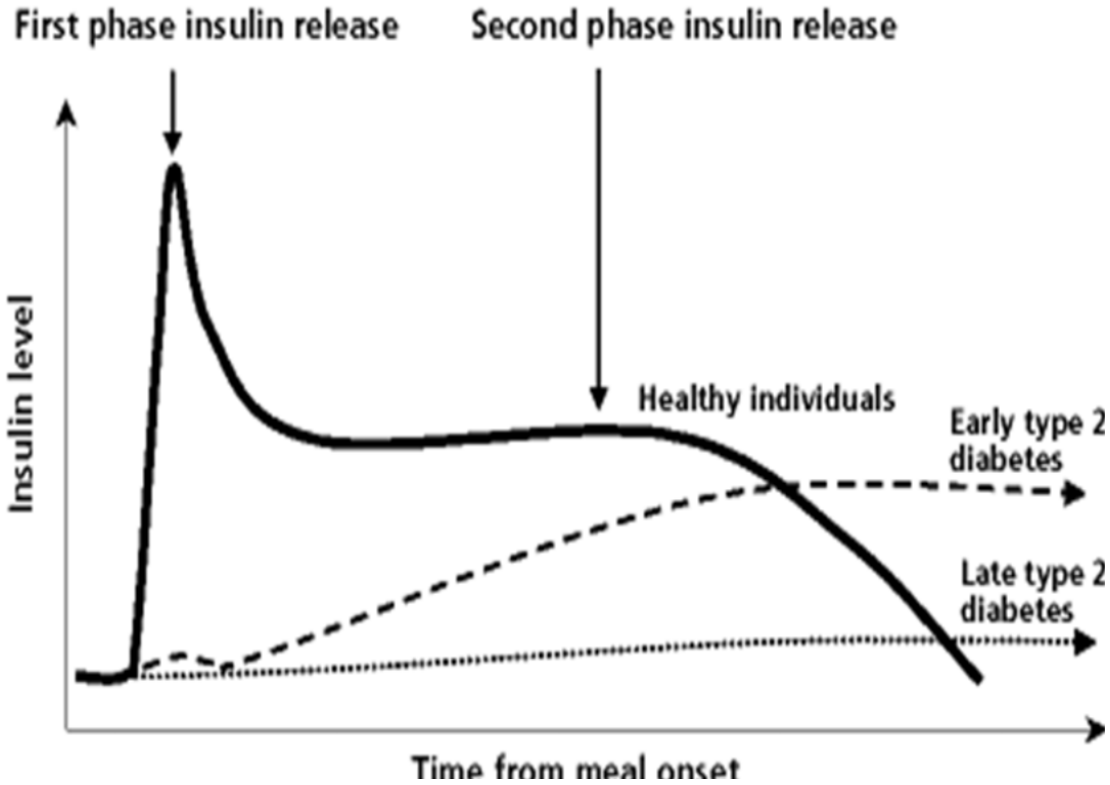
Hyperglycemia is an important factor with respect to the development of complications of diabetes and this is reflected in the fact that a decreased in the average blood glucose can have a profound effect in the prevention of complications. Regarding the glucose pathways, glucose-6-phosphate inside the cell has multiple metabolic fates. The hexosamine pathway accounts for less than 3% of the total glucose used.

Evidence claims that the hexosamine pathway is the main reason for the defect in the glucose utilization that is associated with hyperglycemia. Diminished expression of sarcoplasmic reticulum calcium ATPase in cardiac cells and increased TGFbeta in the vascular smooth muscle cells and endothelial cells occur as a result of enhanced flux through the hexosamine pathway. Hexosamine, for example, glucosamine when incubated with adipose tissue can cause insulin resistance in fat cells. Increased production of glucosamine disrupts the ability of insulin to cause GLUT4 translocation to the surface of the cell.

INSULIN SECRETION AND TYPE 2 DIABETES

The measurement of insulin levels via radioimmunoassay is currently the most widely used method to test beta cell functioning. Though this is widely used nearly 50-60% of the insulin secreted by the pancreas is taken up by the liver even before it reaches the systemic circulation. This standard test also has the disadvantage that it cannot distinguish between endogenous and exogenous insulin. Therefore it cannot reliably detect endogenous beta cell function. Anti-insulin antibodies can add to the inaccuracy of this method.

Insulin is derived from proinsulin that is cleaved by convertases to form the following products: insulin, C peptide, and two pairs of basic amino acids. As C peptide is released in equal proportions and concentrations with insulin and is not taken up by the liver, it may be used as an indicator of endogenous insulin production. However, C peptide has a long plasma half life and this can be a disadvantage as they do not change in the same proportion as the change in insulin secretion rate. Of the total insulin produced, 50% is basal and the remaining is produced in response to meals. There are rapid fluctuations in the secretion of insulin and this profile is also disrupted in individuals with type 2 DM. The physiological importance of this pulsatile secretion, that is the low amplitude but rapid pulse insulin mainly relates to the portal vein and the liver.



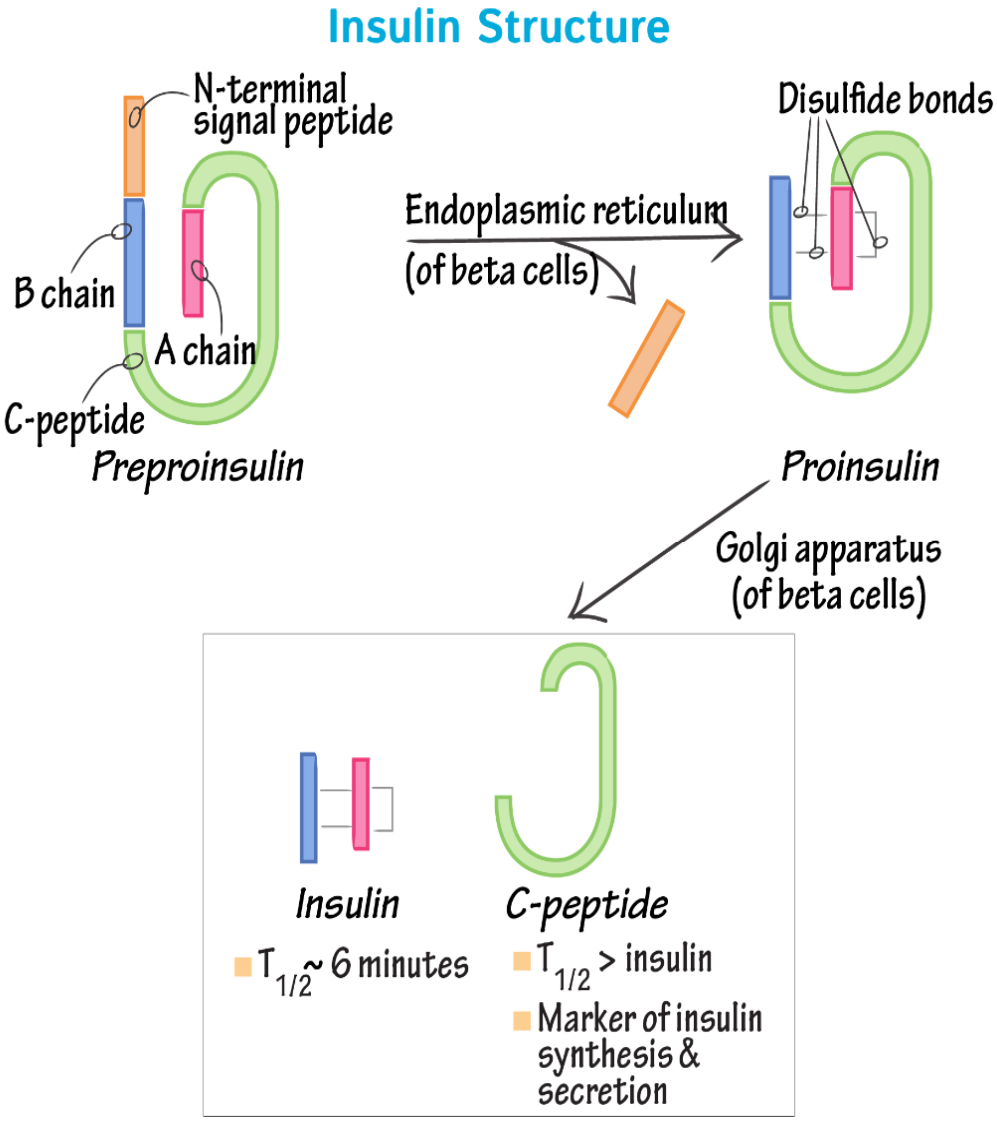
Diurnal variations in insulin secretion were also present. Maximal secretory responses were obtained in the morning when compared to the afternoon or the evening. These diurnal differences highlight the decreased responsiveness of the beta cells to glucose in the later part of the day.

It is the ability of the beta cell to compensate for insulin resistance that determines if the plasma glucose levels will remain normal in an insulin resistant person. This must involve increased secretion of insulin even when normal concentrations of blood glucose are present. For this to occur, it requires an increase in beta cell sensitivity to glucose. This is mainly mediated by two mechanisms. First, an increased quantity of beta cells is found to be present in obesity and other states of insulin resistance. Second, insulin resistance by itself is associated with an increased expression of hexokinase rather than glucokinase in

the beta cell. Since hexokinase has a lower Michaelis constant for glucose when compared to glucokinase it shifts the glucose insulin secretion dose response graphic curve to the left. This results in enhanced insulin secretion over a wide range of glucose concentrations.

Though there is a heightened sensitivity of beta cells to glucose in states of insulin resistance, the degree of both must be matched in order to assess for the adequacy of the compensatory response. A sensitivity index is used for this calculation. It must be remembered that both basal and 24 hour insulin secretion rates are higher by more than 3 fold times in obese people.

In type 2 DM though there is hyperinsulinemia the degree of rise in insulin secretion is not in proportion with the degree of insulin resistance. The beta cell defect in these patients is manifested by an absent first phase insulin response and a diminished second phase insulin response. In type 2 DM increased levels of proinsulin and other conversion products are seen in the serum. This further emphasizes that concentrations of individual peptides must be measured when due to the confounding effects of these other products in the measurement of circulating insulin. The temporal pattern of insulin secretion is altered in patients with type 2 DM. In a 24 hour period, normal subjects produce equal amounts of basal and postprandial insulin. But individuals with type 2 DM produce a greater proportion of basal insulin in comparison to post prandial insulin.



This is because of decreased amplitude of the pulse of insulin that is secreted after meals. The number of pulses remains unaffected but the amplitude of the pulses is diminished. Overall, the pathophysiology of type 2 DM includes insulin resistance, defective insulin secretion increased hepatic glucose production and systemic inflammation.

Initially in the early stages of the disease glucose tolerance is maintained to near normal because of the compensatory increase in insulin. But as the disease progresses, beta cell failure is inevitable and a state of insulin insufficiency develops. When insulin is not present in adequate levels to suppress the synthesis of glucagon, glucagon levels also begin to raise further detoriating carbohydrate metabolism. Hence, both impaired insulin production and insulin resistance can contribute to the pathogenesis of type 2 SM but the relative contribution of each of these variables is not determined.

DIAGNOSIS

The American Diabetes Association outlined certain criteria for the diagnosis of diabetes:

Fasting plasma glucose>=126 mg/dl where fasting is defined
as no caloric intake for 8 hours
OR
2 hours post-prandial glucose>=200 mg/dl during OGTT.
The test should be done as described by the WHO with 75 grams
of anhydrous glucose dissolved in water
OR
HBA1C >=6.5%, done by a method that has been certified by the NGSP.
When there is no unequivocal hyperglycemia, repeat testing will be necessary
OR
When a patient has classic symptoms of diabetes,
a random plasma value>=200 mg/dl

Screening for prediabetes with an assessment of risk factors is to be done even in asymptomatic individuals. For the general population screening begins at 45 years of age and if normal, must be screened at an interval of three years. Certain high risk groups require to be screened irrespective of their age:

- First degree relative with diabetes
- Race/ethnicity
- History of cardiovascular disease
- Hypertension
- Dyslipidemia
- PCOS (polycystic ovarian syndrome)
- Physical inactivity
- Severe obesity, acanthosis nigricans and conditions associated with insulin resistance

In addition to these groups of individuals, patients with prediabetes, (HBA1C>=5.7%, impaired glucose tolerance or impaired fasting glucose) are to be tested annually. Women who have been diagnosed with gestational diabetes mellitus have to be screened every three years once throughout their lives. Type 2 DM may remain undiagnosed for many years as hyperglycemia develops much more gradually and the early stages of the disease are well managed by the innate mechanisms of the body itself. But this does not mean that the undiagnosed patients are at any lesser risk of developing the micro vascular and macro vascular

complications of diabetes. This is especially important because the duration of glycemic burden is a major predictor of adverse outcomes.

PREVENTION

The diabetes prevention program showed that an intensive lifestyle management on the part of the patient itself could lower the risk of developing diabetes by around 58% in a time of three years. There were two goals set by the DPP. One, being a 7% weight loss to be achieved over the first 6 months and the second being 150 minutes of physical activity in one week. This goal of 150 minutes per week was arrived at after calculating the amount of calories one would need to spend for physical activity that is an approximate 700 calories.

Reducing the intake of calories is of great importance though recent research has confirmed that the quality of fats consumed may be more important than the total quantity. If an exercise regimen is to be designed for the prevention of diabetes, it would be probably include both aerobic exercises and resistance

training. Prolonged immobility or a sedantry time is definitely discouraged as breaking up that time has shown to be beneficial in reducing post-prandial glucose values. The beneficial effects of exercise in fact extend to the prevention of gestational diabetes as well.

ASSESSMENT OF GLYCEMIC CONTROL

Self monitoring of blood glucose is an integral part of management of diabetes. This allows patients to evaluate themselves and see if they are actually achieving their targets. This can give self satisfaction to the patients. SMBG accuracy is dependent on the instrument and the user. Patients must be taught how to use the data obtained from SMBG to adjust calories, exercise or medications. It is especially important in the monitoring of hypoglycemia in diabetics. For patients with type 2 DM on a less intensive insulin regimen, frequent monitoring of blood glucose may be useful as the frequency is directly proportional to the chance of meeting HBA1C goals. Continuous glucose monitoring measures interstitial glucose which correlates well with plasma glucose and is very useful in the management of brittle diabetes.

The HbA1C testing reflects average glucose levels over 3 months and is a major determinant of the complications of diabetes. This test is to be performed in all patients with diabetes at the beginning of the assessment as well as for the monitoring of the disease. Any condition which can alter the RBC turnover may cause discrepancies in this test. Examples of such conditions include hemolytic anemias, blood transfusions, agents stimulating erythropoesis, and pregnancy.

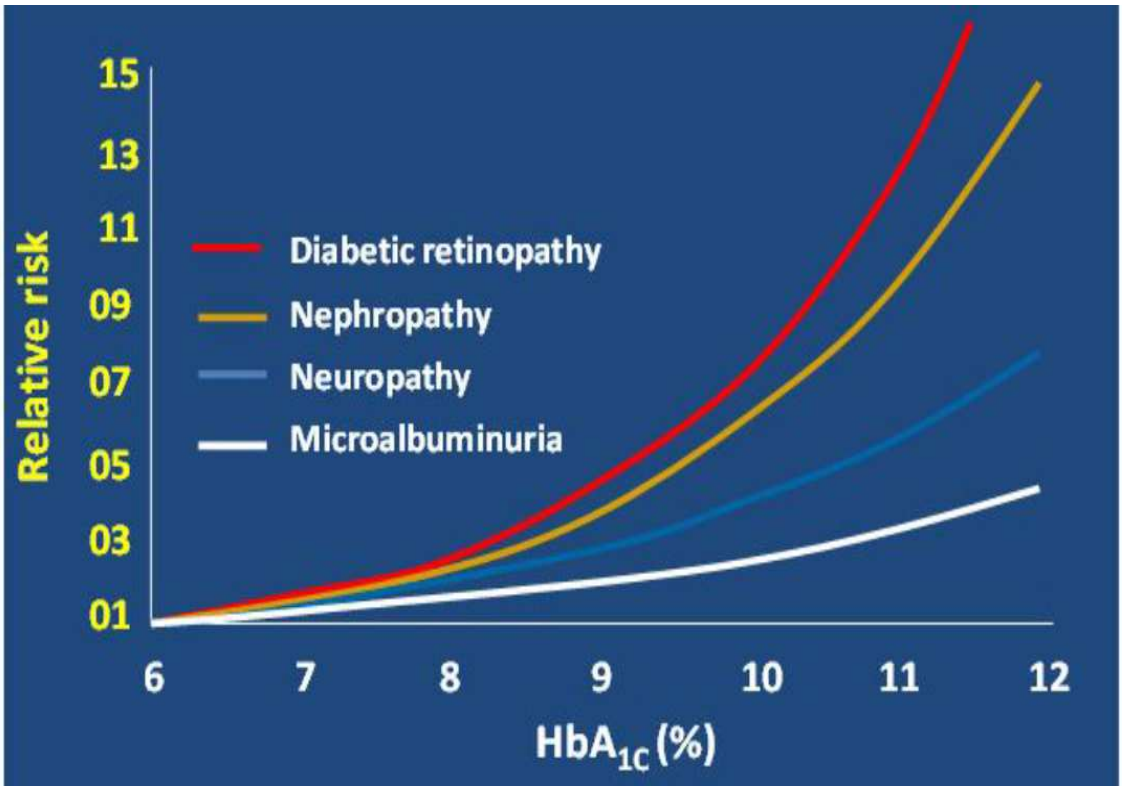
Hemoglobin variants can severely alter the HbA1C levels. The disadvantage of this test is that it does not provide an insight into the glycemic variability of the patient or the risk of hypoglycemia.

Regarding the goals for HbA1C a reasonable goal for most patients would be 7%. Even more stringent control such as 6.5% may be set but the risks of hypoglycemia must be kept in mind. Stringent control of HbA1C values is associated with a delay in micro vascular complications and further lowering of HbA1C from 7 to 6% makes the absolute risk of complications much smaller. But with the recent trend of polypharmacy in type 2 DM the risks of these lower glycemic targets easily outweigh the benefits.

Though micro vascular complications increase the morbidity of life it is cardio vascular disease that contributes to the maximum mortality. The ACCORD trial(Action To Control Cardiovascular Risk In Type 2 Diabetes) compared intensive and standard glycemic control and also intensive versus standard blood pressure control and the use of fenofibrate along with statins to check for a reduction in the outcome of cardiovascular events. But it had to be terminated early due to greater mortality in the intensive glycemic control arm. Also, the other two arms of intensive blood pressure control or the use of a fibrate showed no significant benefit. The 10 year follow up of the VADT has shown a reduction in the number of cardiovascular events but no benefit with respect to mortality.

Thus it can be concluded that patients with a long history of duration of diabetes, high risk groups, advanced atherosclerosis, and old age people may not

benefit from very aggressive targets and their safety must be kept in mind while trying to conquer the disease.



Hypoglycemia episodes must force the clinician to re-evaluate the regimen of the patient. Symptoms of hypoglycemia are irritability, hunger, confusion, cognitive impairment, sweating and tachycardia but the symptoms are not limited to the ones mentioned above. Clinically significant hypoglycemia is defined as blood glucose values less than 54 mg/dl.

Although 54 mg/dl is the set value an alert value of 70 mg/dl may be used to avoid the risks of symptomatic hypoglycemia. Treatment involves the immediate ingestion of glucose or carbohydrate containing foods. The acute response is better with glucose rather than carbohydrates but any form of carbohydrate that contains glucose is enough. In patients with Type 2 DM,

ingested proteins increase the insulin secretion in the body without concomitantly increasing plasma glucose concentrations. Therefore carbohydrate foods which are rich in protein are not to be used in the treatment of hypoglycemia.

For those who cannot consume carbohydrates by the mouth, glucagon is indicated.

POINT OF CARE HbA1C TESTING

Any stressful event can worsen the diabetic control and precipitate ketoacidosis. In the event of such emergency complications, adjustment of the treatment regimen is required and temporary insulin may also be necessary.

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

- **OBESITY MANAGEMENT**
- **PHARMACOLOGICAL MANAGEMENT**
- **CARDIOVASCULAR DISEASE AND RISK MANAGEMENT**

OBESITY MANAGEMENT

There is strong evidence that proper obesity management can prevent or significantly delay the progression from prediabetes to diabetes. This benefit is more often observed early in the natural history of diabetes when obesity is the main reason for insulin resistance and has caused some reversible beta cell dysfunction but the insulin secreting capacity of the individual has remained normal. At every visit, BMI should be documented.

Diet, physical activity and behavioral therapy are advised for those overweight and obese individuals who are mentally ready to undergo weight loss of more than 5%. This requires a high intensity intervention and atleast a 500-750 kCal/day deficit. Diets must be individualized. For those people who achieve the short term goals, a long term comprehensive weight loss program may be initiated. This includes monthly contact, continued use of a reduced calorie diet and high intensity physical activity for atleast 200-300 minutes per week. For those who desire a weight loss of more than 5%, short term interventions with a very low calorie diet, such as <=800kCal/day and even total meal replacements can be prescribed. But these patients are to be carefully selected by medical practitioners and are also to be kept under close monitoring. The look AHEAD

trial did not show that strict lifestyle interventions such as obesity management could reduce cardiovascular events but it did show that those who had intensive lifestyle management required fewer glucose lowering, pressure lowering and lipid lowering medications. Further other benefits of weight loss included improvements in physical and sexual functioning.

The various diets prescribed for diabetes may differ in their composition but it is enough if they create the necessary energy deficit. The choice of diet is to be individualized.

Regarding pharmacological treatment of obesity physicians must first consider their choice of anti-diabetic agent. Those medications that promote weight loss may be given a preference. Such agents include metformin, alpha glucosidase inhibitors, SGRT inhibitors, GLP-1 agonists, and amylin mimetics. Insulin and thiazolidinediones and insulin secretagogues are associated with gain of weight. DPP-4 inhibitors are said to be weight neutral.

The objective of weight loss medications is to help patients adhere to a strict diet and exercise regimen. These are in fact contraindicated in women who are pregnant or aim to get pregnant.

There are only a few drugs that have been approved by the Food and Drug Association for the treatment of obesity. The drugs have been classified into those used for short term treatment and those used for long term management of obesity.

Drug	Dose	Average weight loss in 1 year relative to placebo	Adverse effects
Phentermine	8 mg tds	-	Headache, insomnia, hypertension
Orlistat (lipase inhibitor)	60-120 mg tds	3.4 kg	Abdominal pain, flatulence, liver failure and oxalate nephropathy.
Selective serotonin agonists Lorcaserin	10 mg bd	3.2 kg	Hypoglycemia, headache, fatigue, serotonin syndrome suicidal ideation
Phentermine and Topiramate combination	15 mg/92 mg qd	8.9 kg	Paresthesias, xerostomia, headache.
Naltrexone and Bupropion combination	32/360 mg bd	4.1 kg	Nausea, constipation, depression, vomiting
Liraglutide	3 mg sc qd	5.9 kg	Hypoglycemia, nausea, vomiting.

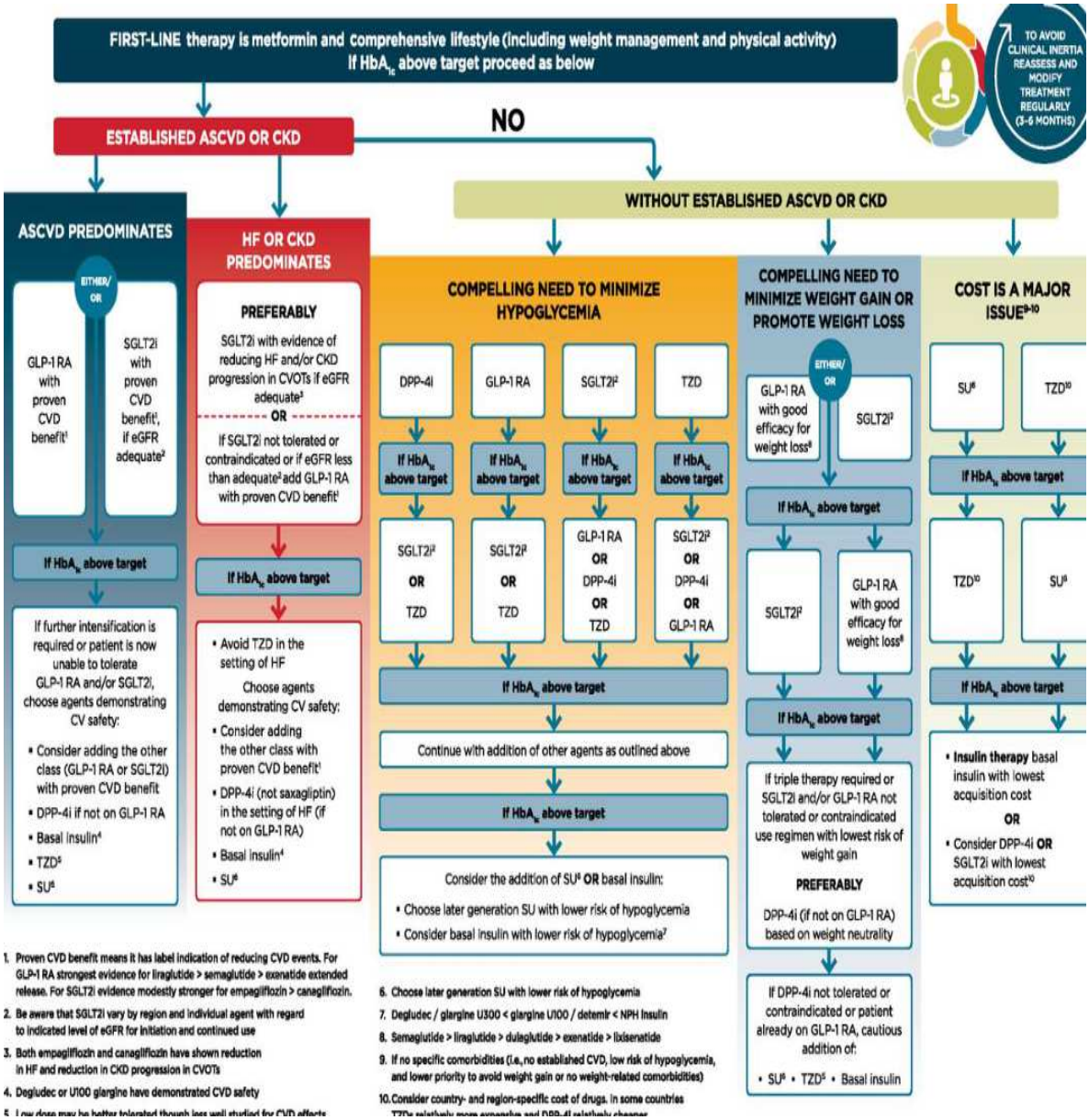
Weight loss medications are indicated for patients with a BMI >= 30 or >=27 with one or more obesity associated comorbidity. Metabolic surgery can be recommended as a treatment option in those with a BMI >=40, or >=35 if blood sugar levels are uncontrolled with pharmacological management. It is also seen that those who undergo surgery maintain glycemic control for atleast 5 -15 years. Concerns include dumping syndrome, vitamin and mineral deficiencies, anemia, osteoporosis and sometimes severe hypoglycemia.

PHARMACOLOGICAL MANAGEMENT

As of today, there are a wide variety of choices available to treat diabetes. The preferred first line agent in the management of diabetes is metformin. Unless and until there are contraindications monotherapy with metformin shall be the universal protocol. Metformin is not just safe but also effective and inexpensive.

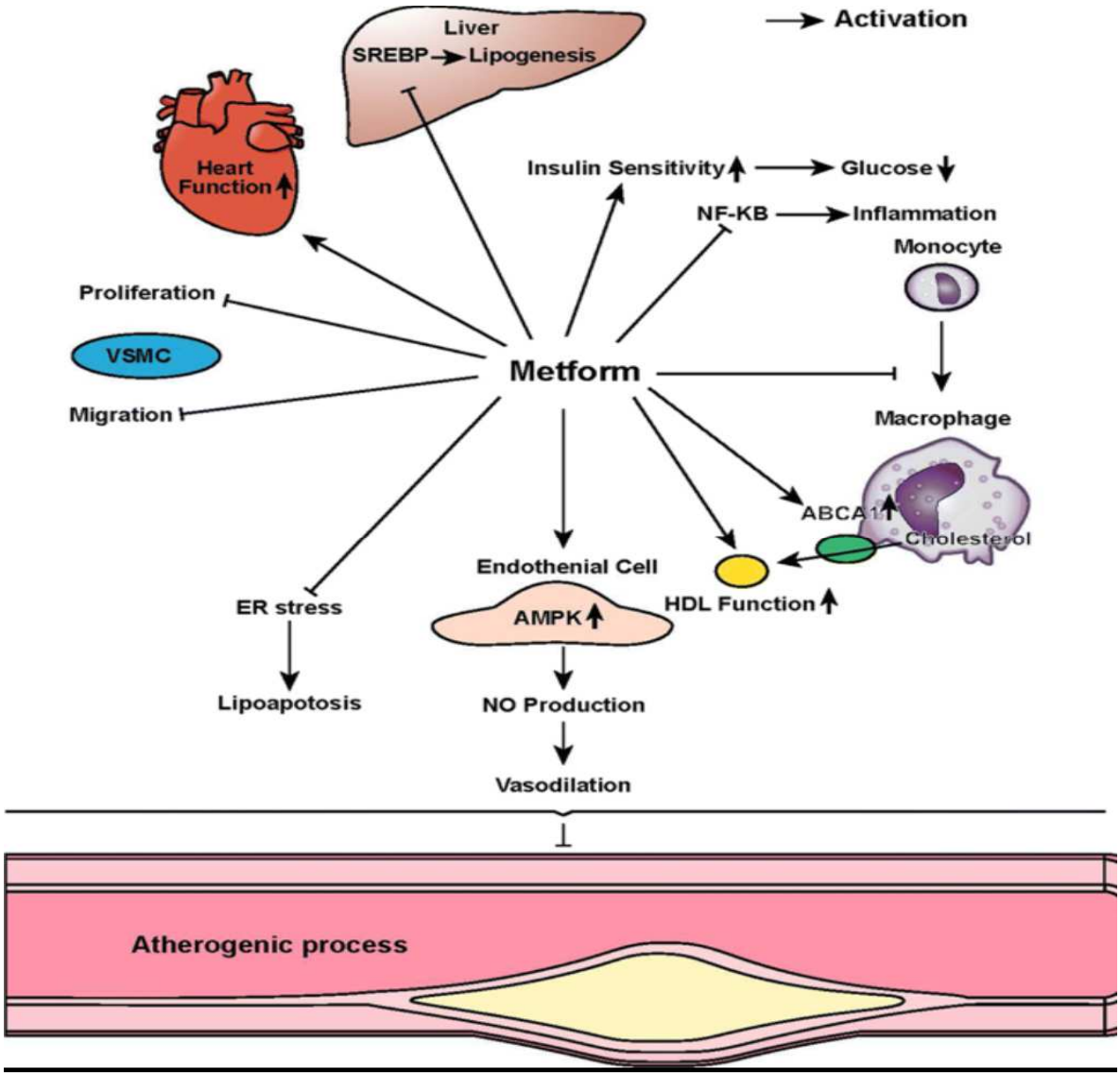
One may consider initiating insulin therapy in newly diagnosed type 2 DM who are symptomatic or those who have mean plasma glucose levels more than 300 mg/dl. In those diabetics with an HbA1C of more than 10, again insulin therapy is essential. When HbA1C levels are more than 9%, dual therapy may need to be initiated.

If after three months of treatment the prescribed drug or drugs do not help in maintaining the HbA1C levels to the desired limit, then, consider adding another agent. Continuous evaluation of the regimen is frequently needed to prevent lack of compliance with respect to the patient.



METFORMIN

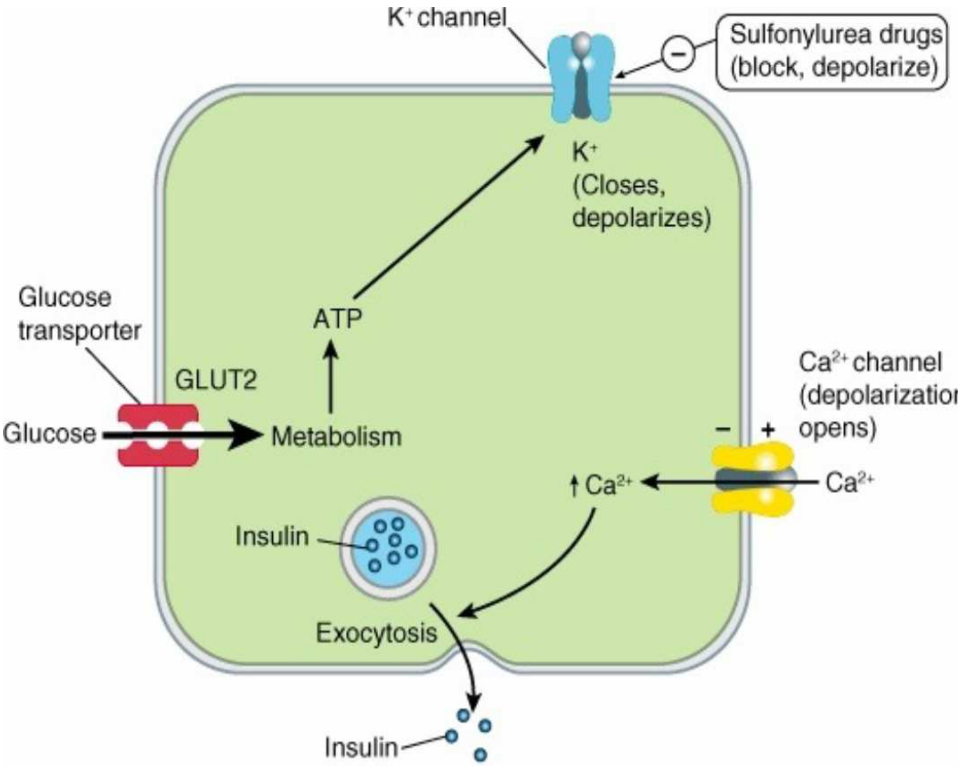
Biguanides act primarily by reducing hepatic glucose production via activation of AMP-activated protein kinase. Other minor mechanisms include impairment of renal gluconeogenesis, decreasing the speed of glucose absorption, enhancing the conversion of glucose to lactate by the enterocytes, directly stimulating glycolysis in tissues, improving glucose removal from the blood and reducing plasma glucagon levels.



The most important feature is that their glucose lowering action is independent of the functioning of beta cells, and that is why they rarely ever produce hypoglycemia. Metformin has a half-life of around 1.5-3 hours and is excreted by the kidneys. In patients with kidney disease, lactic acidosis is a feared complication. The most common adverse effects of metformin are the gastrointestinal side effects. They are not only dose related but also transient. As vitamin B12 absorption is affected annual screening is recommended. It cannot be initiated in patients with an eGFR of less than 30.

SULFONYLUREAS

The main action of this group of drugs is to increase the release of insulin from the pancreas. Long term administration of these agents may decrease serum glucagon levels which contribute to their hypoglycemic effect. The first generation SUs includes Tolbutamide, Chlorpropamide, and Tolazamide and these are outdated at present.



The second generation drugs are glyburide, Glipizide and Glimepride. These are basically highly efficacious drugs which are neutral to cardiovascular or kidney disease, are of a low cost, associated with weight gain, and have a risk of inducing hypoglycemia.

Meglitinides include Repaglinide and Nateglinide that act closing potassium channels on beta cells and functioning as insulin secretagogues. As Repaglinide has no sulphur in its structure it may be used in diabetics with allergy to sulpha group of compounds.

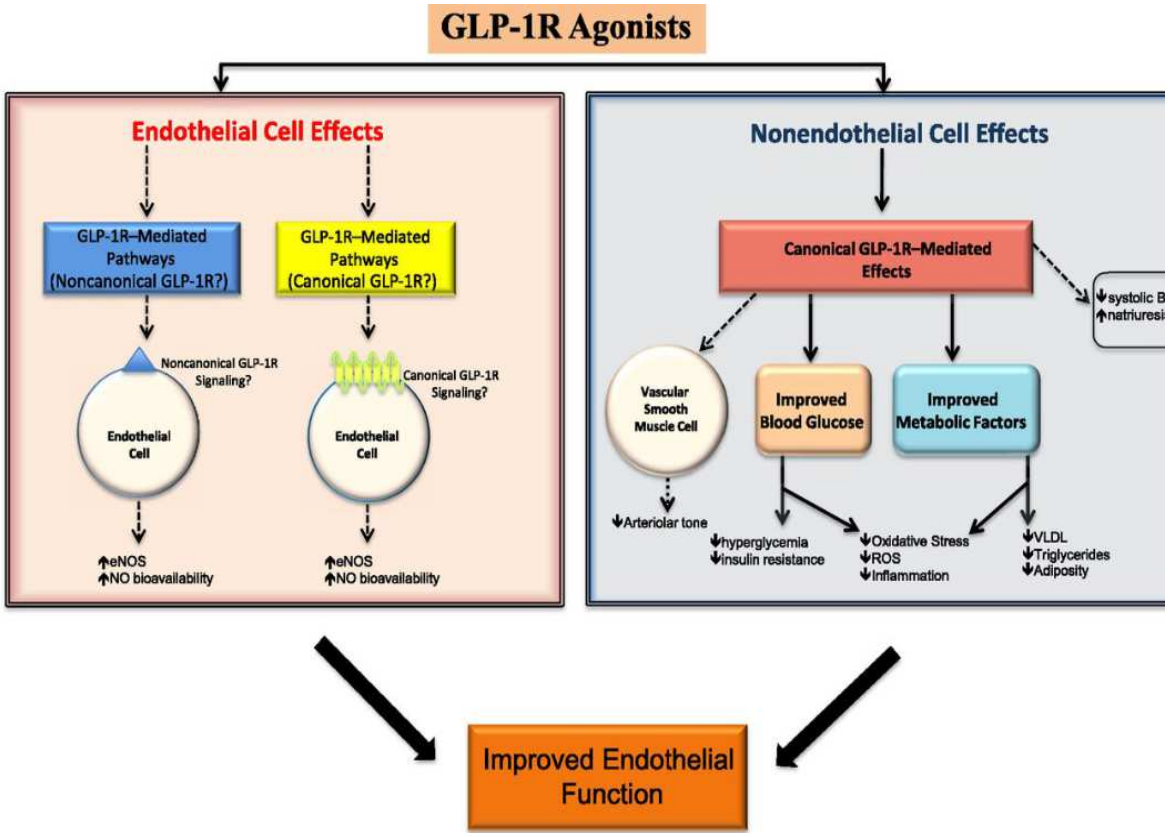
THIAZOLIDINEDIONES

They are ligands of PPAR-gamma, which is a part of the thyroid family of receptors. The PPAR receptors are found in the muscle and liver and fat. They modulate the expression of the genes involved in various metabolisms, and also the genes involved in insulin signal transduction. They also play a role in the genetics of adipocyte differentiation. A triglyceride lowering effect is seen with Pioglitazone which also has an adverse effect of increasing the risk of bladder cancer, whereas Rosiglitazone carries more cardiovascular risk than Pioglitazone and is recommended only in a selected group of population when blood sugar cannot be adequately controlled by other mechanisms. An adverse effect common to both is fluid retention which can worsen heart failure and are associated with weight gain.

They don’t have a risk of hypoglycemia. Pioglitazone is believed to have some benefit with respect to cardiovascular disease. They are of benefit in non alcoholic steato-hepatitis. Their low cost is probably what can be quoted as their most attractive feature.

GLP1-RA

Glucagon-like-peptide 1 receptor agonists are an upcoming class of drugs. In type 2 DM, the release of Glucagon like peptide is actually reduced after meals. This effect is important as GLP suppresses glucagon production and hepatic glucose output. These drugs have a number of mechanisms of action; suppressing post meal glucagon release, increasing glucose induced insulin secretion, slowing gastric emptying, and a central loss of appetite. It also increases the beta cell mass.

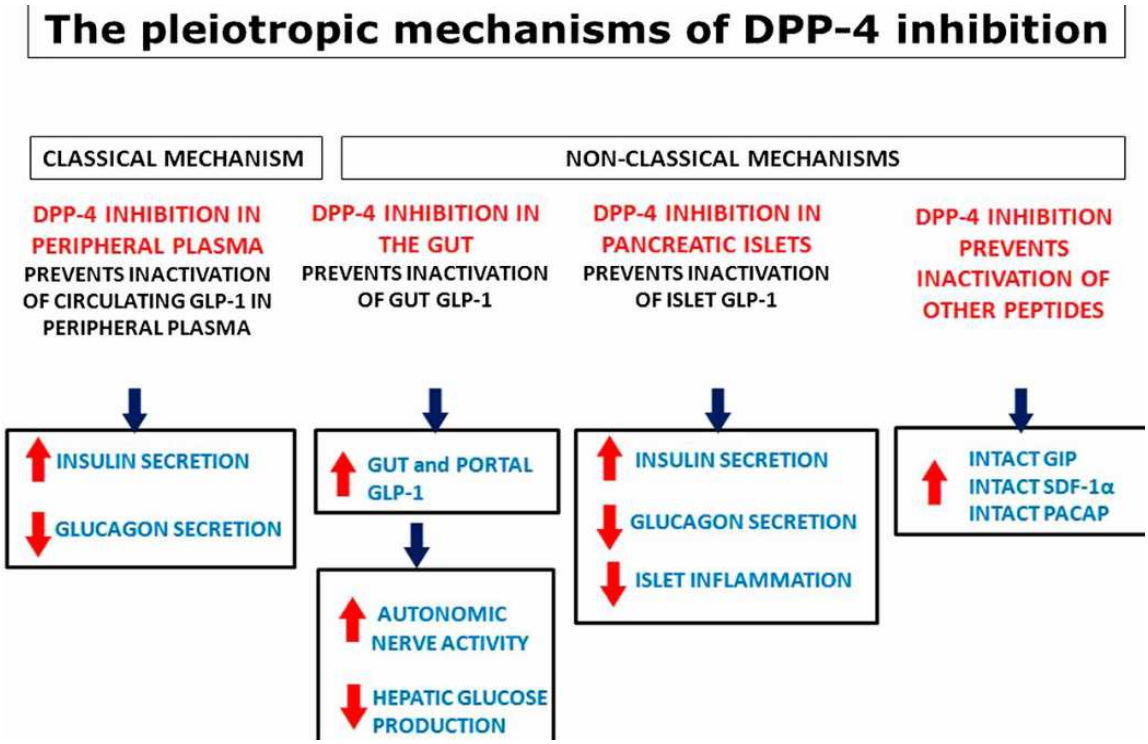


These drugs are also highly efficacious, with an almost negligible risk of hypoglycemia. They are associated with weight loss and are in fact used for the management of obesity. They have a cardio protective effect and can be used in those patients with a high risk of cardiovascular disease with Liraglutide showing

the best results. Administered as subcutaneous injections, their disadvantage is their high cost. Liraglutide is also beneficial in halting the progression of diabetic kidney disease. There is an increased risk of thyroid tumors and acute pancreatitis apart from the common gastrointestinal side effects.

DPP-4 INHIBITORS

Sitagliptin, Saxagliptin and Linagliptin are inhibitors of dipeptidyl peptidase 4 enzyme which performs the function of degrading incretin hormones such as GLP. Hence these drugs increase circulating levels of GLP which decreases post-prandial glucose elevations. Sitagliptin has an oral bioavailability of 85%and reduces HbA1C from 0.5-1%.



Linagliptin is the most recently approved drug among the three and has been used for monotherapy as well.

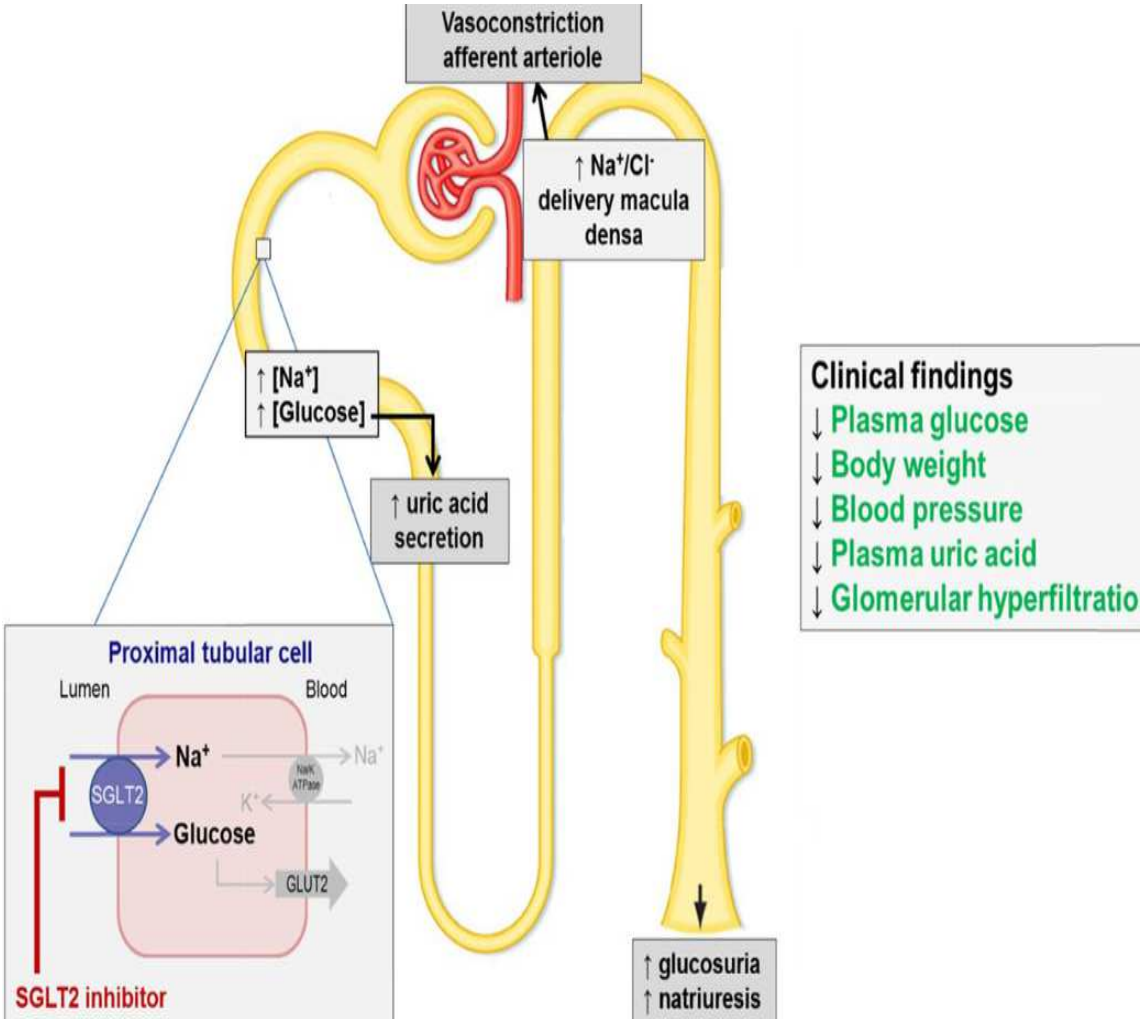
The efficacy of these drugs is intermediate but they usually do not cause hypoglycemia. They are weight neutral and are also neutral with respect to cardiovascular disease and renal disease. They are not cost effective and there is also a potential risk of acute pancreatitis associated with their use.

SGLT-2 INHIBITORS

This group of drugs is also known by the name of Glifozins and they mainly function by inhibiting glucose reabsorption in the kidney via sodium glucose transport protein 2. Canaglifozin, Empaglifozin and Dapaglifozin are some of the drugs belonging to this class. Of the three, Canaglifozin was the first SGLT-2 inhibitor to be approved for use. Functional pancreatic beta cells are not necessary for the action of SGLT-2 inhibitors and hence they can be used even in late stages of type 2 DM. SGLT-2 is expressed in the kidney, brain, liver, muscle, thyroid and heart. They are excreted in urine as inactive metabolites.

Apart from the glucose lowering action, they have multiple effects. They are protective against atherosclerosis, obesity, hyperlipidemia, and also have anti-neoplastic activities. They can deactivate the rennin-angiotensin-aldosterone system.

It is better to avoid initiating these drugs when eGFR is less than 60 and stop them altogether when it is less than 30.



They have an intermediate range of efficacy. There is no risk of hypoglycemia. Weight loss is the usual rule. They have a potential benefit in reducing the risk of cardiovascular disease and are also of benefit in heart failure patients. Empaglifozin followed by Canaglifozin are the best drugs which also slow down the progression of diabetic kidney disease. Canaglifozin cannot be used when the eGFR is below 45 and Empaglifozin when the eGFR is below 30.

Adverse effects include an increased risk for amputations which is the nightmare for most diabetic patients and hence many clinicians double think before prescribing this drug.

But it has clearly been proven in recent studies that the benefits outweigh the risks. The most common and troublesome adverse effect is the frequent genitor-urinary tract infections and the precipitation of euglycemic ketosis. There is also an increased risk of bone fractures.

ALPHA GLUCOSIDASE INHIBITORS

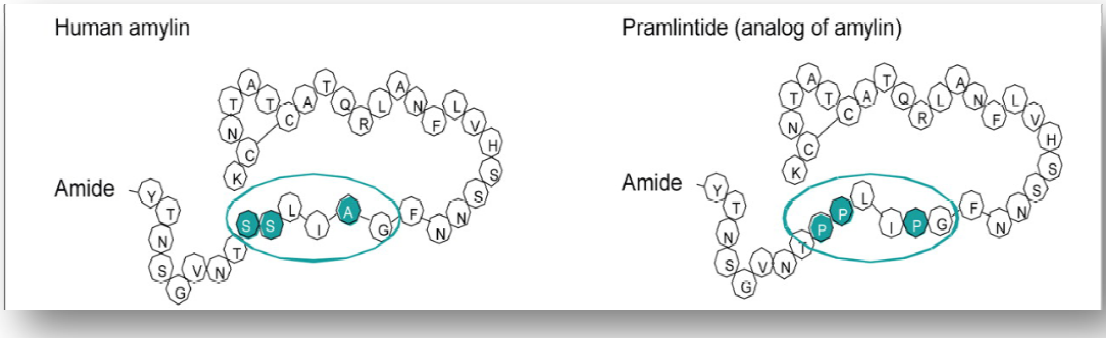
The enzyme alpha glucosidase facilitates carbohydrate digestion in the upper gastrointestinal tract. It is attached to the brush border of the intestinal cells and breaks down complex carbohydrates into individual monosaccharides. When inhibitors of this enzyme are given they function by slowing the intestinal absorption of complex carbohydrates and allowing only monosaccharides such as glucose and fructose to be transported out into the blood stream. Miglitol is more potent than acarbose. When digestion is minimized post meal hyperglycemia can be controlled. Major adverse effects are flatulence, diarrhea and abdominal pain. The undigested carbohydrate present in the bowel is fermented by bacteria releasing gas. They are excreted via the kidney and hence cannot be used in renal failure.

BILE ACID SEQUESTRANTS

Colesevelam hydrochloride was developed as a cholesterol lowering drug but also has an anti-diabetic action by interrupting the entero-hepatic circulation and decreasing the activation of Farnesoid X receptor. It may also impair glucose absorption. It is not to be used in patients with a history of pancreatitis.

AMYLIN ANALOGUE

Pramlintide is an amylin analogue which alters post-prandial glucose levels and can be used in both types of diabetes. It suppresses glucagon release and mediates anorectic effects through the central nervous system. It delays gastric emptying. Administration is through subcutaneous route. It cannot be mixed with insulin during injection.



INSULIN

Insulin is a small protein with 51 amino acids in two chains A and B with disulphide bonds. The goal of subcutaneous insulin therapy is to be a replica of the physiological pattern of insulin secretion as much as possible.

Rapid acting insulin- three rapid acting analogues, insulin lispro, aspart and glulisine are available. They can be taken before the meal and help in controlling

post-prandial glucose levels. Their duration of action is around 4-5 hours. This also decreases the risk of post meal hypoglycemia.

Short acting insulin- regular insulin belongs to this class and is made by recombinant DNA techniques to resemble human insulin as closely as possible. Its onset of action begins in 30 minutes, and duration lasts for 5-8 hours. When short acting insulin is injected subcutaneously, the hexamers break down to form dimmers and finally monomers. Thus there are three rates of absorption with the final monomeric phase being the fastest. As a consequence of this, when regular insulin is given, there is an early post-prandial hyperglycemia with a slightly increased risk of late post-meal hypoglycemia.

Intermediate-acting insulin- NPH insulin is formed by combining insulin and protamine in equal proportions so that neither will be present in an uncomplexed form. The duration of action is for 4-12 hours.

Long-acting insulin- Insulin glargine is a soluble insulin. The maximum activity is maintained for a period of up to 24 hours or even longer. It is given once daily. It cannot be mixed with other insulin solutions as the preparation is acidic. Insulin detemir has the most reproducible effect.

Today insulin can be delivered via portable pen injections, continuous subcutaneous insulin infusion devices and standard delivery systems such as conventional subcutaneous injections.

Basal insulin is initiated at a dose of around 10 units/day and the dose is adjusted by 2-4 units once or twice weekly if the target fasting blood glucose is not attained. If control is not possible with basal insulin alone, one may either add rapidly acting insulin before the largest meal starting with 4 units and gradually increasing the dose by 1-2 units per week. The other options are to add a GLP-1 RA or change to premixed insulin twice daily. The ongoing basal insulin dose of the patient is split into two thirds and one thirds and the dose is altered by 1-2 units to attain the target.

Inhaled insulin may be used to control post meal hyperglycemia. It is contraindicated in all patients with any evidence of chronic lung disease. Spirometry is a must before beginning this therapy. Even in those patients on combined injectable insulin therapy, metformin is to be continued.

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

Blood pressure is to be monitored regularly and if elevated must be brought down to target levels of 130/80. An ACE inhibitor will obviously be the first choice for treatment of hypertension in diabetes and especially microalbuminuria. Saturated fat, trans-fat and cholesterol intake are to be reduced. Increased fiber diet and physical activity is recommended. For those patients who are not already on statin therapy, it is best to obtain a fasting lipid profile at the time of the first visit.

2016 ADA guidelines for statins in DM

Table 8.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

For all diabetic patients with atherosclerotic heart disease use of high intensity statins is indicated. For people more than 40 years of age with diabetes

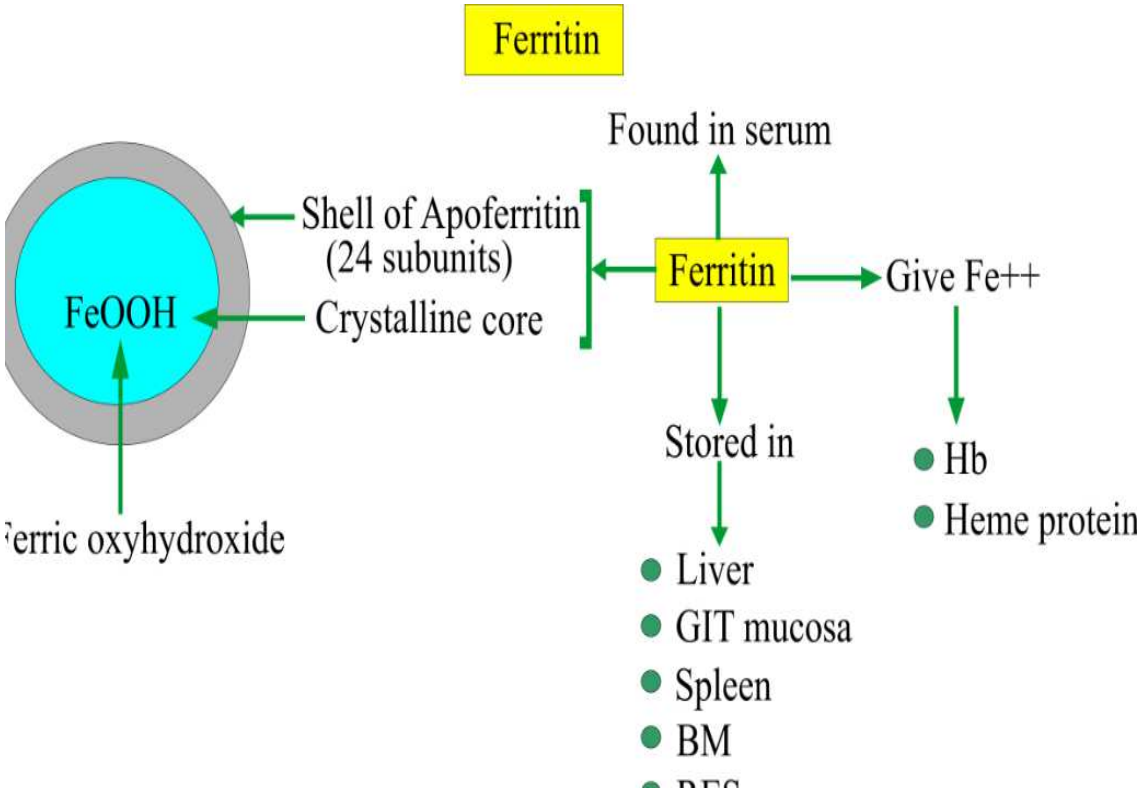
but no atherosclerotic disease moderate intensity statin will be the choice of therapy. For those diabetics less than 40 years of age with no atherosclerotic disease no statins are required. If LDL cannot be brought down to target levels of 70 mg/dl with the highest possible statin dose, addition of ezetimibe may be advised. In patients with diabetes and a history of atherosclerotic disease aspirin can be used as secondary prevention.

FERRITIN

Ferritin is the storage form of iron and is one of the first laboratory values to get affected in the earliest stage of iron deficiency. It is a globular protein with 24 subunits. Ferritin that is not found in combination with iron is called apoferritin. Free iron aids in the formation of free radicals also known as the reactive oxygen species through the Fenton reaction. Ferritin concentrations rise in response to stress implying that it is an acute phase protein. Low ferritin is an indicator of iron deficiency, but also may indicate hypothyroidism, vitamin C deficiency or celiac disease.

Increasing concentration of iron and ferritin inside the cells can lead to insulin resistance and beta cell dysfunction. In addition to this, diabetes itself being a state of chronic low grade systemic inflammation may elevate serum ferritin levels. Since ferritin is a marker of body iron stores whose catalytic reactions just as discussed above could lead to lipid peroxidation, and lipid peroxidation may be involved in causing insulin resistance ferritin levels may be high in diabetes. Secondly, it is believed that iron is directly involved in insulin

signaling. Serum ferritin ranges from 50-200 micrograms/L. adult males have an average serum ferritin of around 100 whereas adult females averaging around 30. When iron stores are depleted, the ferritin falls to below 15. Iron related insulin resistance can be improved by inducing a state of iron depletion. In fact, there have been studies on improvement of insulin sensitivity and insulin secretion after phlebotomy in those who had high ferritin type 2 DM. A statistically significant improvement in insulin sensitivity and secretion has been demonstrated in the therapeutic group. Thus the mechanisms for improved insulin sensitivity especially in the peripheries should be further investigated into. Similarly high ferritin levels in the beginning of pregnancy are also associated with a higher risk of gestational diabetes mellitus (GDM).



SIGNIFICANCE OF SERUM FERRITIN

- A study by NG Forouhi on how elevated serum ferritin will predict the onset of newly diagnosed type 2 diabetes mellitus concluded significantly that serum ferritin is an important determinant.

- A study by JM Fernandes-Real in 2002 showed how phlebotomy is of benefit in improving insulin sensitivity in type two diabetes mellitus, especially as most of them had high serum ferritin levels.

- A study by TP Tuomainen tested the association between body iron and glucose homeostasis indices. It was a cross-sectional population study. It was noted that fasting serum insulin concentration was much higher in those with an elevated serum ferritin. The study finally concluded that mildly elevated body iron stores were also associated with a significant change in the glucose homeostasis indices.

- The Camden study showed a positive association between high serum ferritin levels in the beginning of a pregnancy and risk of development of gestational diabetes mellitus.

- A study done by Rui Jiang showed that heme-iron intake is associated with an increasing risk of diabetes mellitus. Total iron intake, or heme iron from non red meat sources did not however show a positive correlation.

- A study done by Swapnil Rajpathak documented 459 cases of type 2 DM. during the entire follow up period of 20 years, it was found that heme iron intake in women was significantly associated with an increasing risk of diabetes mellitus. It was a prospective cohort study.

- A cross-sectional study done by Megan Jehn in 2004 examined the relation between ferritin, insulin resistance and the development of metabolic syndrome. The study population was around 6044. Exclusion criteria had hemochromatosis in the list. Insulin resistance was defined by measuring fasting insulin levels. At the end of the study it was documented that those with higher serum ferritin levels were more liable to develop metabolic syndrome and insulin resistance than those with low serum ferritin levels, even after adjustment for age, race, BMI, smoking, and alcohol intake.

- Nam Hee Kim did a study on serum ferritin in healthy and diabetic subjects and showed that serum ferritin had a positive correlation with fasting blood sugar levels. The results suggested that serum ferritin could not only be used as a marker of diabetes control but also as a marker of insulin resistance in both controls as well as the subjects.

- F Sharifi did a study on the relationship between HbA1C and serum ferritin levels and showed that ferritin levels in diabetic patients were high but had no correlation with HbA1C.

- Paul cutler did a major study on deferoxamine therapy in type 2 DM and showed that all glycemic parameters improved when serum ferritin levels were lowered in patients with high ferritin type 2 diabetes.

- A meta-analysis concluded that elevated serum ferritin levels are very useful in identifying individuals who are at a high risk of developing type 2 DM.

Serum ferritin is measured by Radio immuno-assay technique and HbA1C was also tested by the same method.

MATERIALS AND METHODS

METHODOLOGY

SOURCE OF DATA

The patients admitted in the Rajiv Gandhi Government General Hospital affiliated to the Madras Medical College from January 2019- June 2019 were enrolled in our study. 50 patients, confirmed to be cases of diabetes mellitus through the American Diabetes Association criteria, who consented to be a part of this study, were accordingly enlisted.

Cases: 50 patients with Type 2 diabetes confirmed by the ADA criteria

Controls: Age and sex matched controls (50 in number) who are non diabetic and do not have any of the confounding factors mentioned in the exclusion criteria.

STUDY DESIGN

A Case-control study

INCLUSION CRITERIA

Patients with type 2 diabetes mellitus according to ADA criteria:

- Fasting plasma glucose levels more than 126 mg/dl OR
- 2 hour post-prandial plasma glucose levels more than 200 mg/dl after an Oral glucose tolerance test with 75 gram anhydrous glucose dissolved in water OR
- HbA1C >=6.5% OR

- Random plasma glucose levels more than 200 mg/dl
- Patients more than 25 years of age

EXCLUSION CRITERIA

- Patients with acute or chronic inflammation
- Patients with autoimmune conditions.
- Patients on immune-suppressive drugs
- Patients on steroid therapy
- Patients with type 1 diabetes mellitus

PRINCIPAL INVESTIGATIONS

- Complete blood count
- Renal function test
- Fasting blood glucose
- Post-prandial blood glucose
- HbA1C
- Serum ferritin

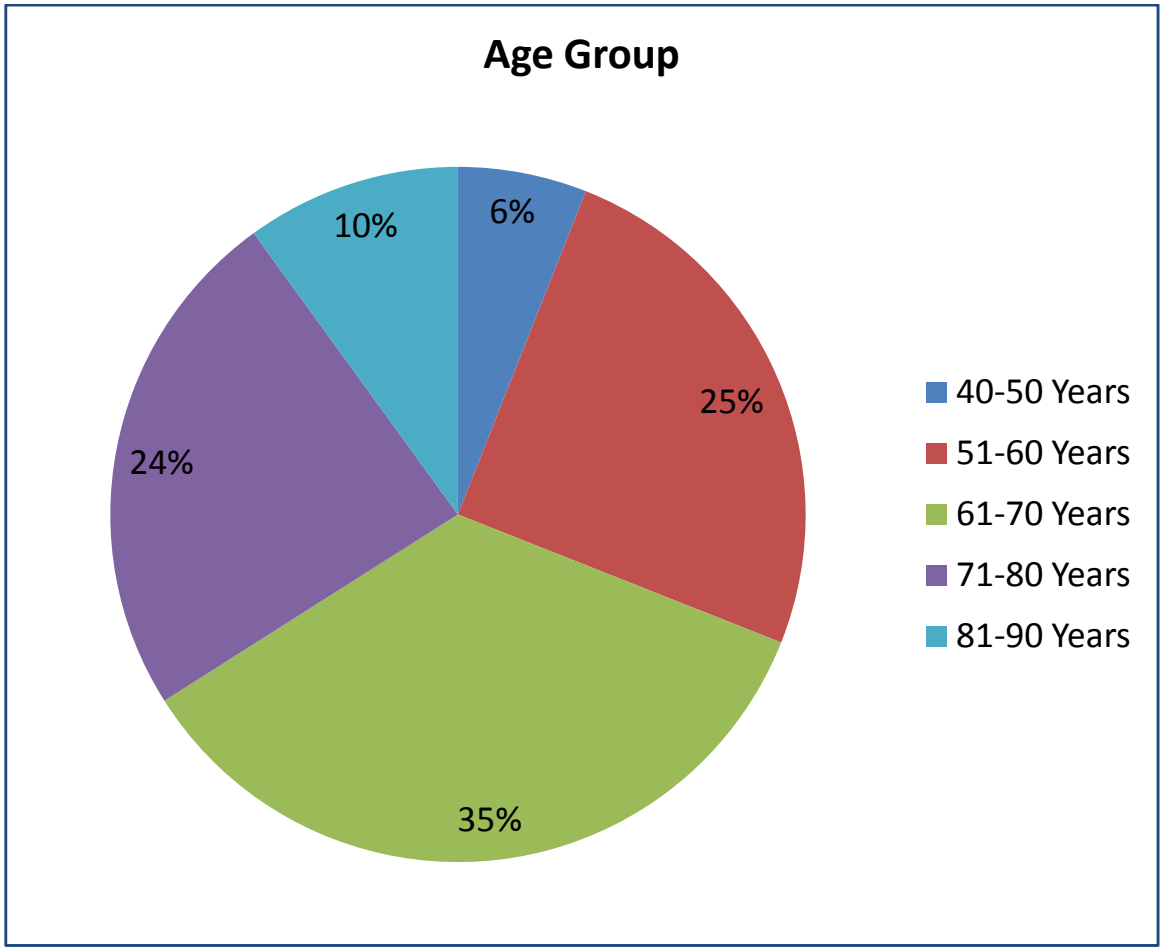
RESULTS AND OBSERVATIONS

RESULTS AND OBSERVATIONS

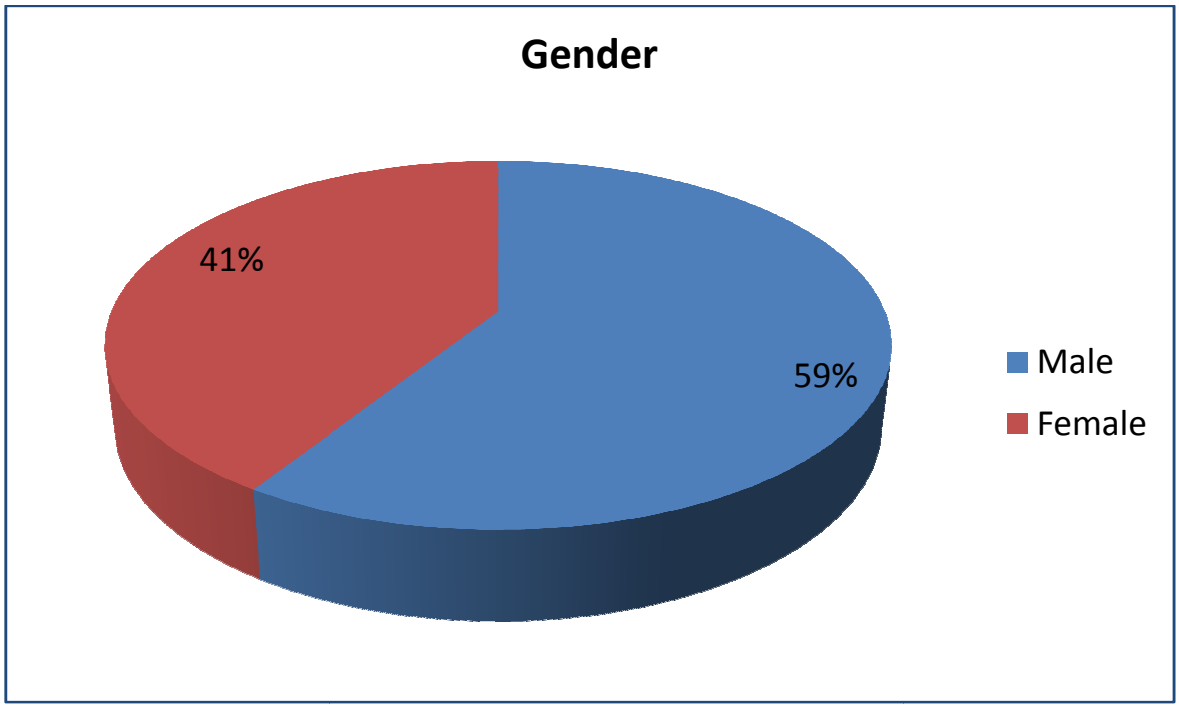
Frequency Table

AGE GROUP	FREQUENCY	PERCENT
40-50 Years	6	6.0
51-60 Years	25	25.0
61-70 Years	35	35.0
71-80 Years	24	24.0
81-90 Years	10	10.0
Total	100	100.0

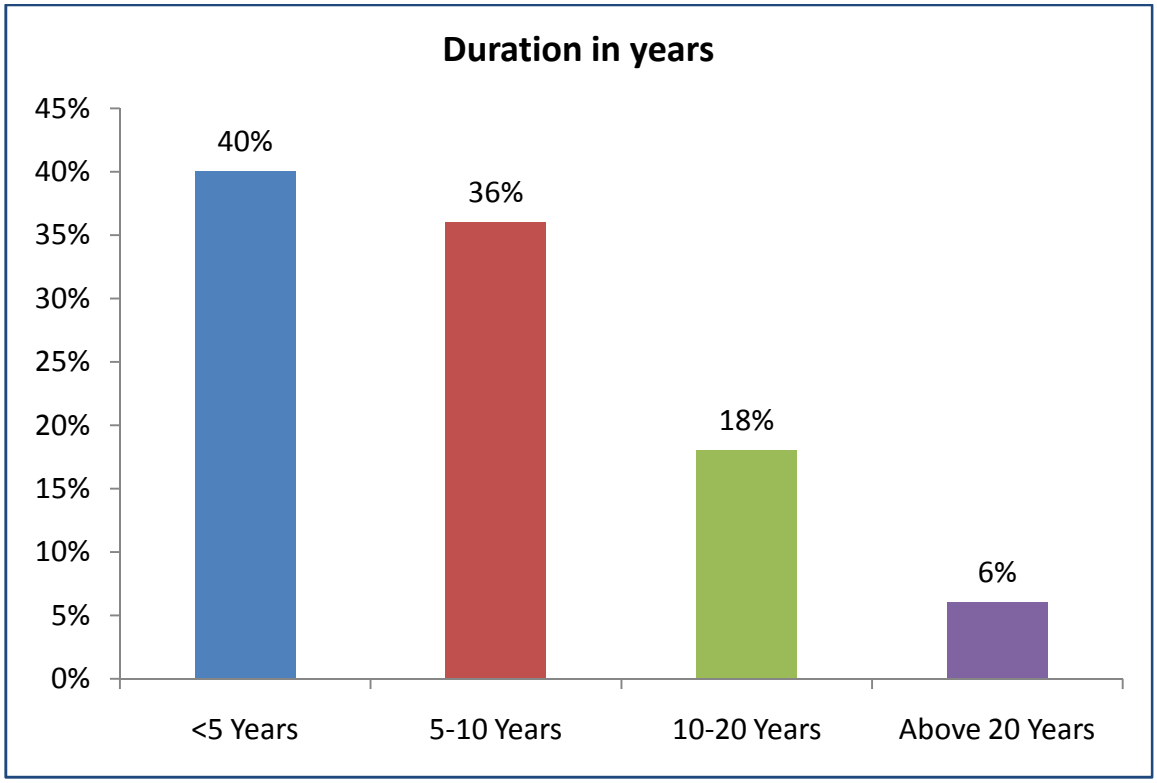
DESCRIPTIVE STATISTICS					
	N	Minimum	Maximum	Mean	Std. Deviation
age	100	44.00	85.00	65.5900	10.21199



GENDER	FREQUENCY	PERCENT
Male	59	59.0
Female	41	41.0
Total	100	100.0

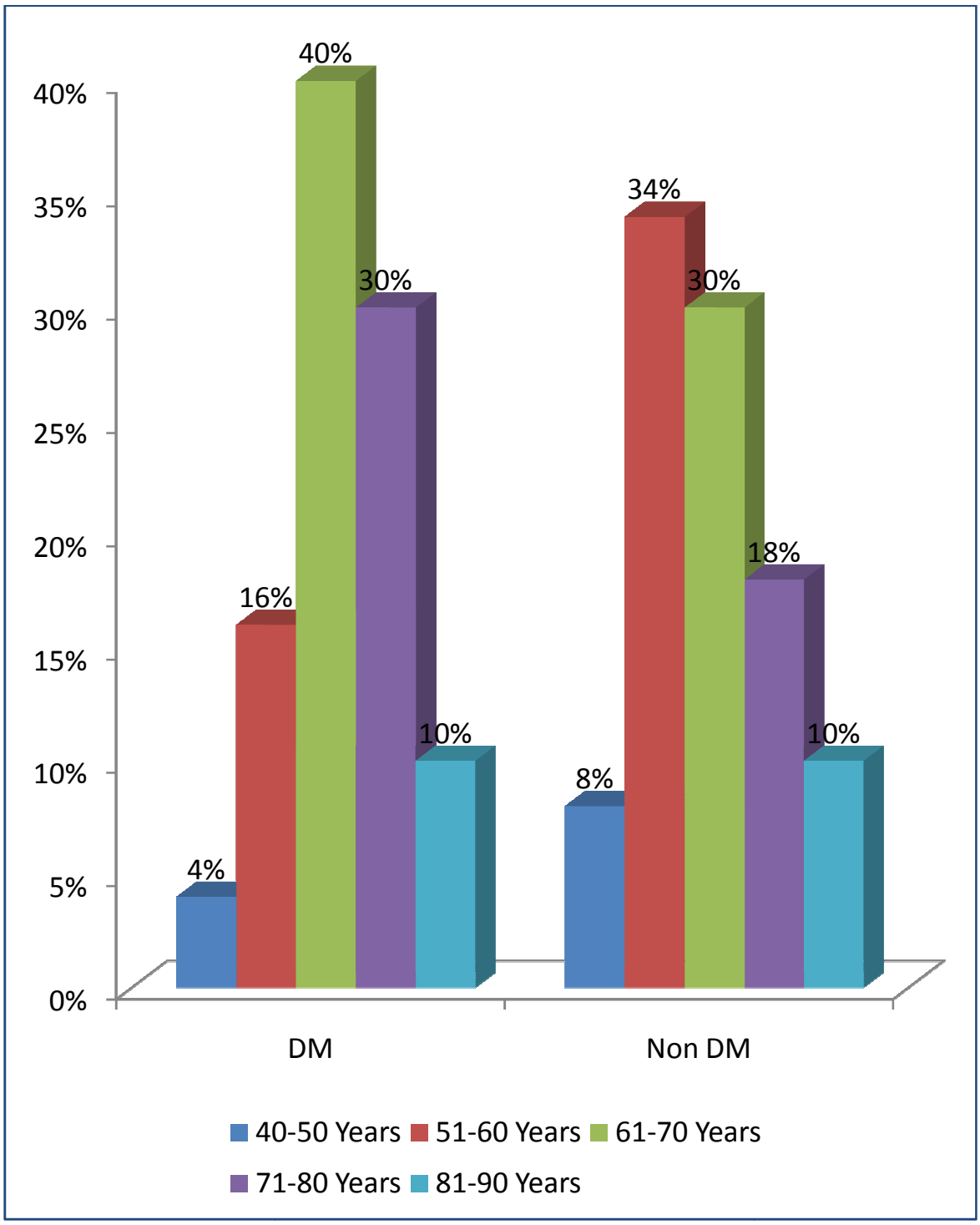


DURATION IN YEARS GROUP	FREQUENCY	PERCENT
<5 Years	20	40.0
5-10 Years	18	36.0
10-20 Years	9	18.0
Above 20 Years	3	6.0
Total	50	100.0



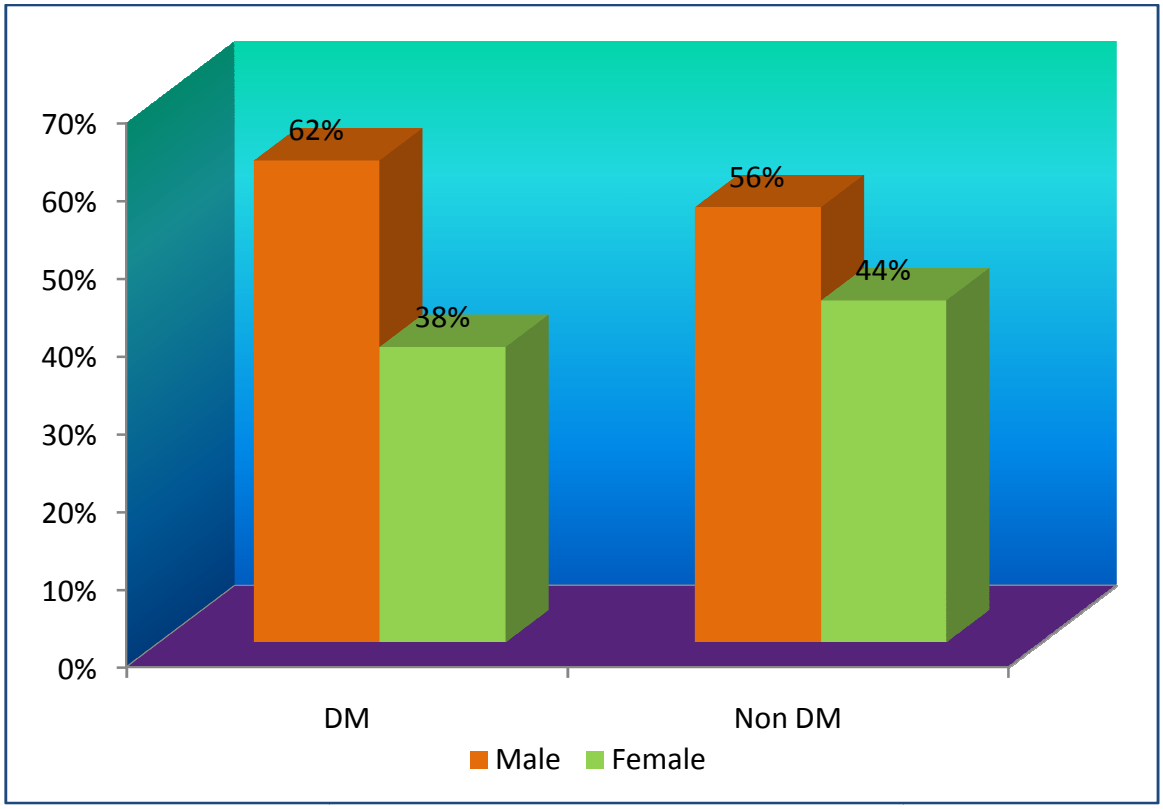
Crosstab				
Age group		**Group**		**Total**
		DM	**Non DM**	
40-50 Years	Count	2	4	6
	% within Group	4.0%	8.0%	6.0%
51-60 Years	Count	8	17	25
	% within Group	16.0%	34.0%	25.0%
61-70 Years	Count	20	15	35
	% within Group	40.0%	30.0%	35.0%
71-80 Years	Count	15	9	24
	% within Group	30.0%	18.0%	24.0%
81-90 Years	Count	5	5	10
	% within Group	10.0%	10.0%	10.0%
Total	Count	50	50	100
	%within group	100%	100%	100%

Pearson Chi-Square=6.121 p=0.190


40%
35%
30%
25%
20%
15%
10%
5%
0%
4%
16%
40%
30%
10%
8%
34%
30%
18%
10%
DM
Non DM
40-50 Years
51-60 Years
61-70 Years
71-80 Years
81-90 Years

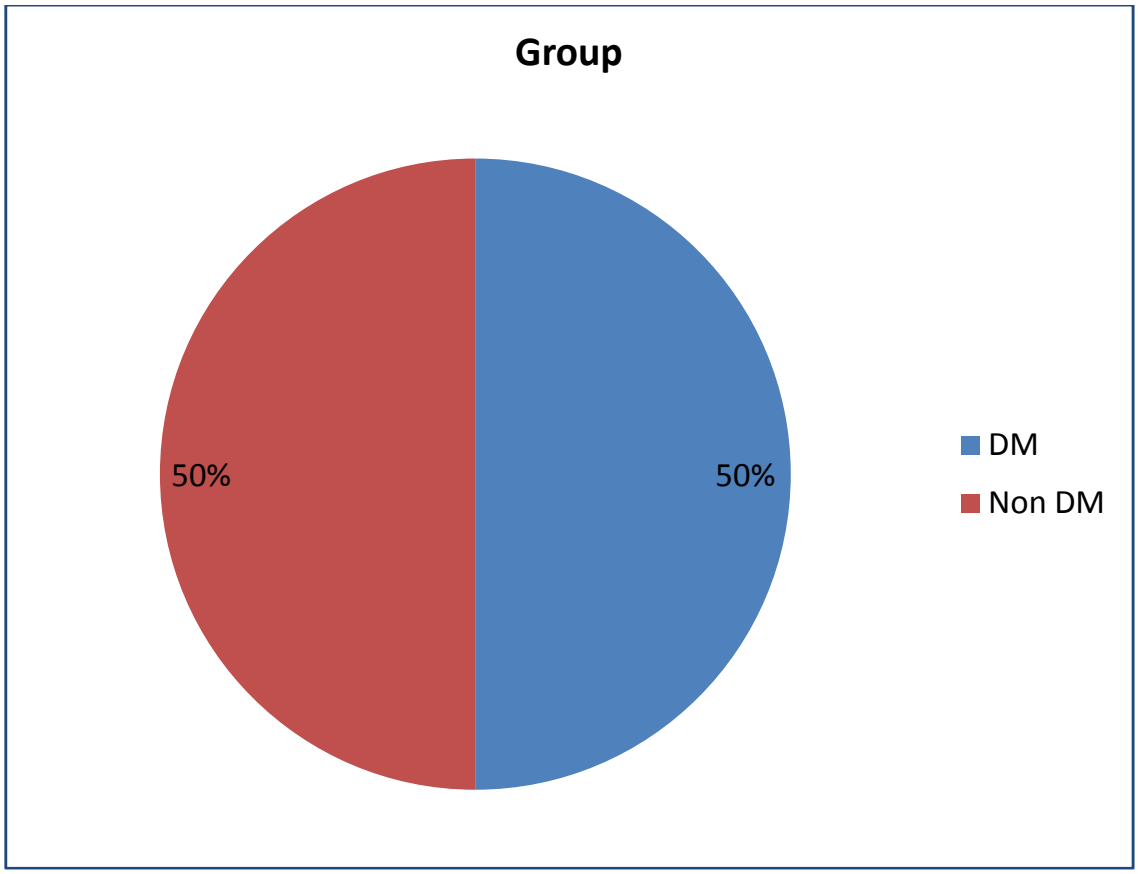
Crosstab				
Gender		**Group**		**Total**
		DM	**Non DM**	
Male	Count	31	28	59
	% within Group	62.0%	56.0%	59.0%
Female	Count	19	22	41
	% within Group	38.0%	44.0%	41.0%
Total	Count	50	50	100
	% within Group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.372 p=0.542



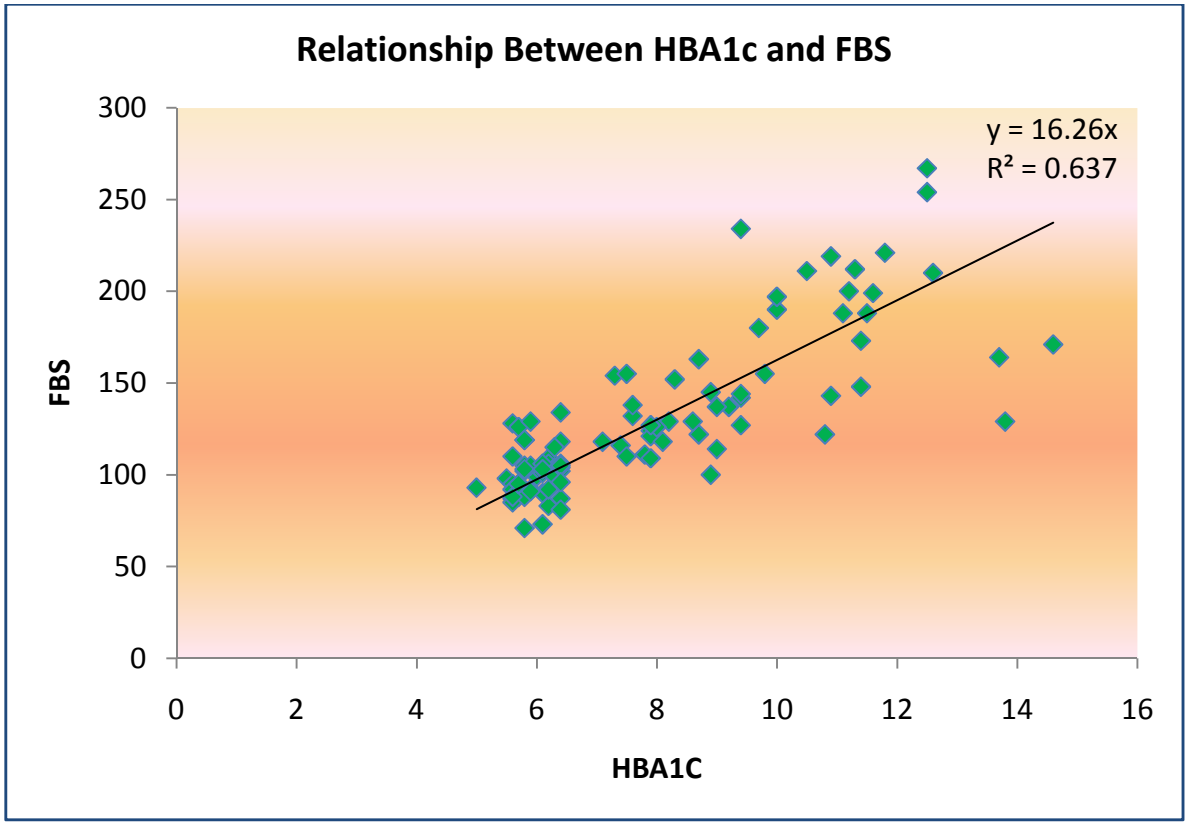
Comorbidities	Frequency	Percent
None	53	53.0
Alzheimers	2	2.0
Cad	8	8.0
Cad,Ckd,Hypertension	1	1.0
Cad,hypertension	6	6.0
Cad, nephropathy	4	4.0
Ckd	2	2.0
Ckd, hypertension	1	1.0
Hypertension	8	8.0
Hypertension, Old CVA	3	3.0
Hypothyroidism	1	1.0
Nephropathy	7	7.0
Old CVA	3	3.0
Seizure disorder	1	1.0
Total	100	100.0

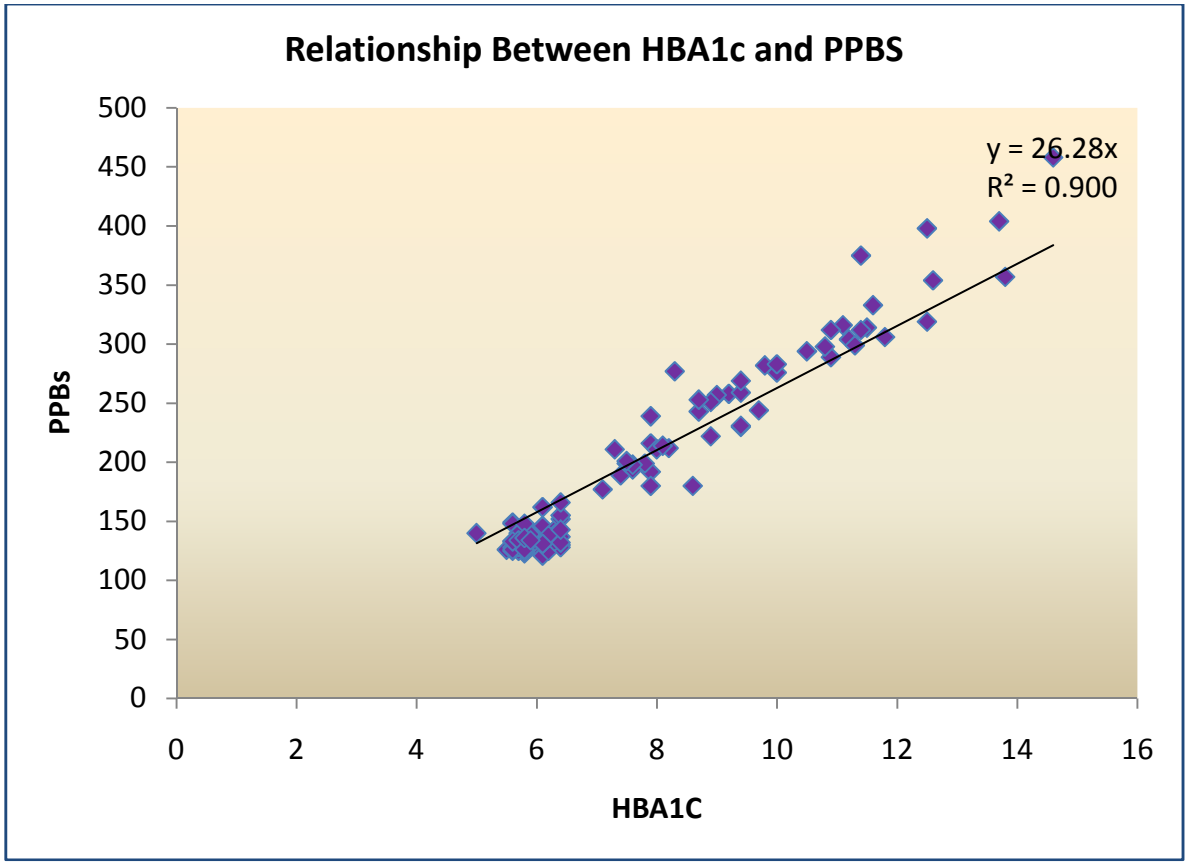
Group	Frequency	Percent
DM	50	50.0
Non DM	50	50.0
Total	100	100.0

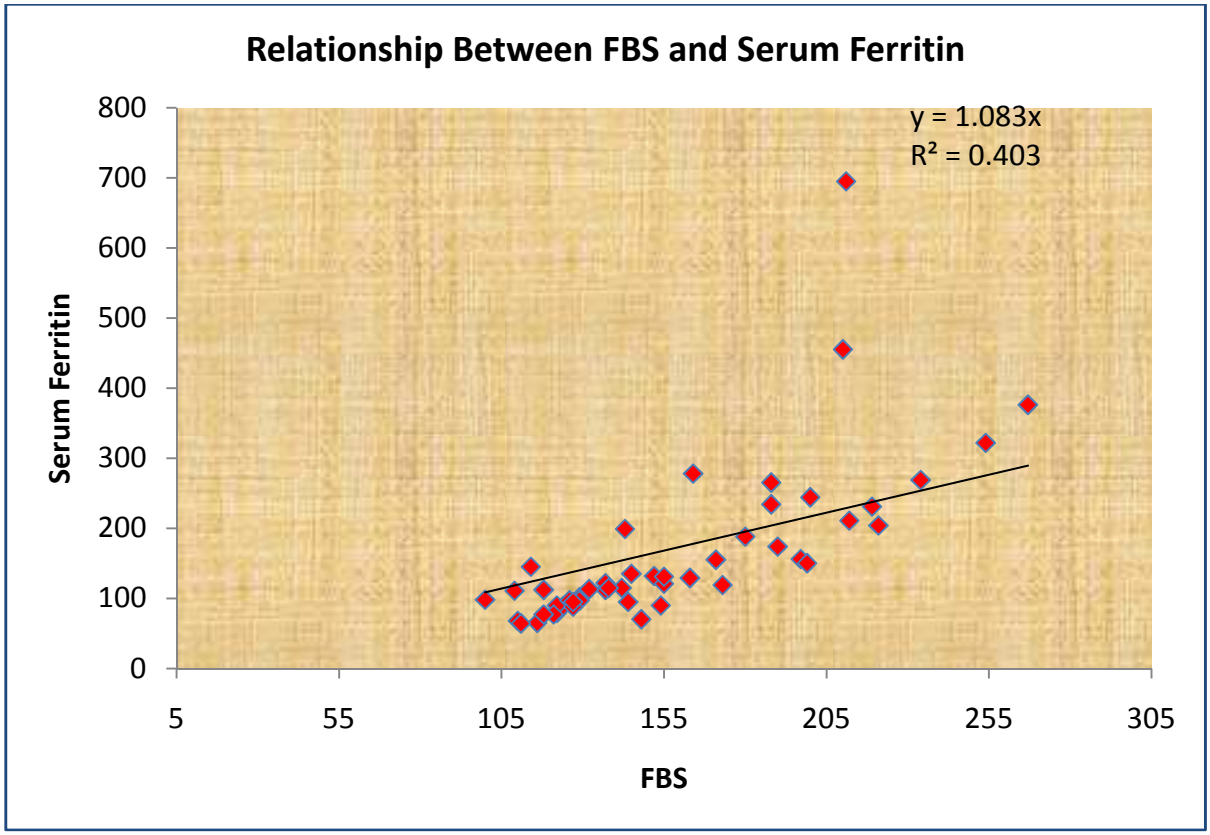


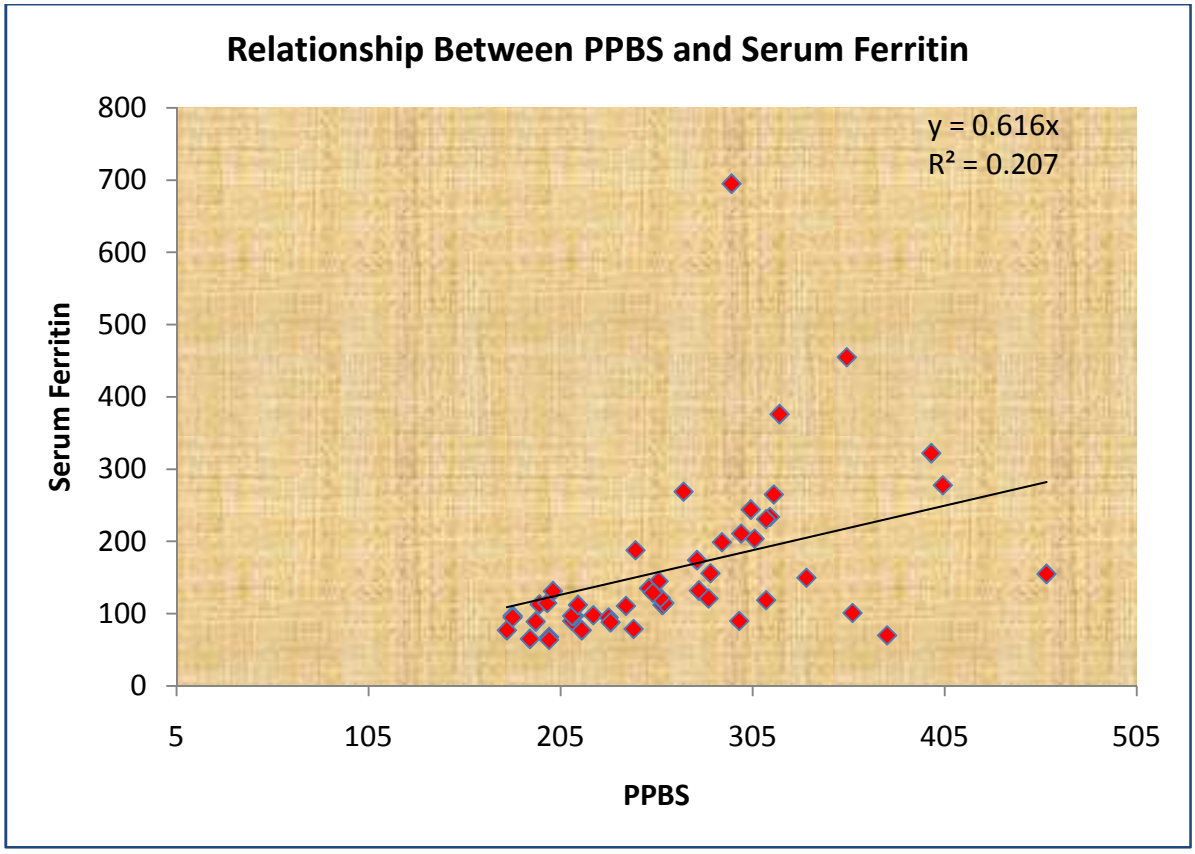
Comparison of Values for Two Groups

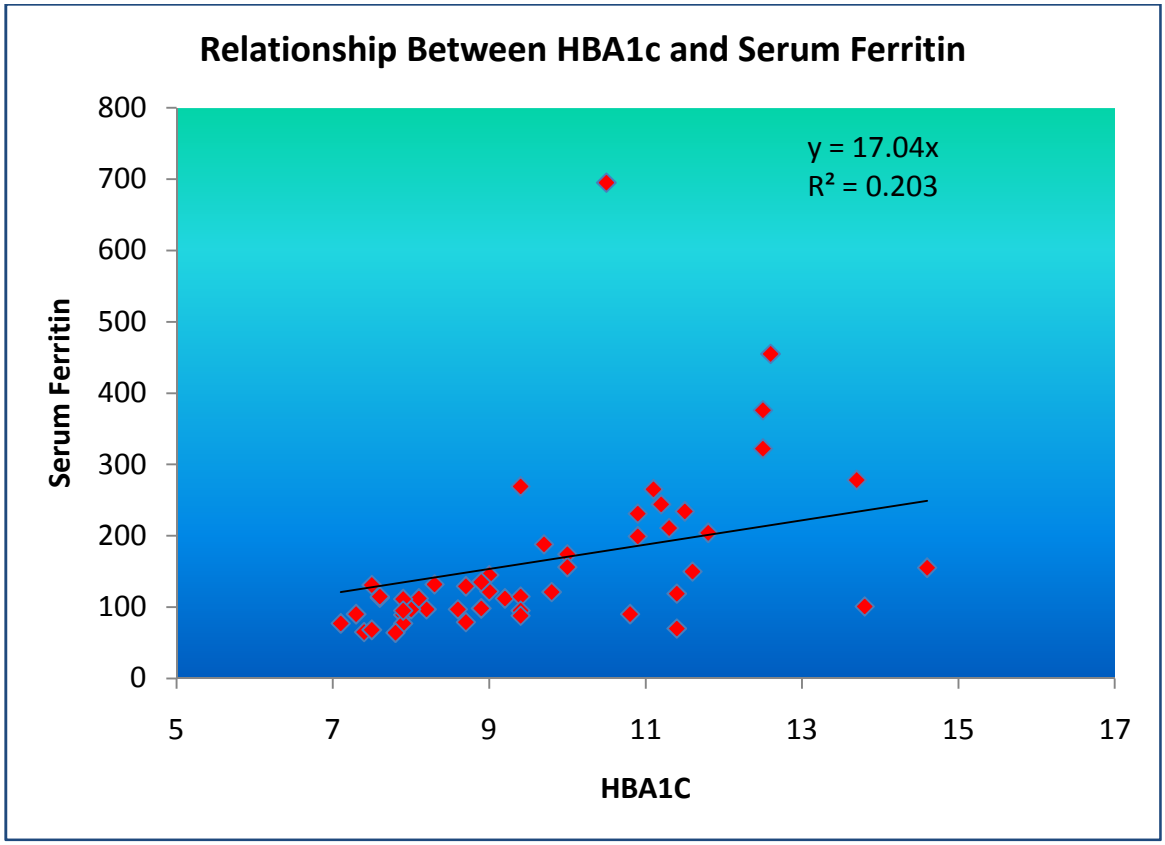
Group		N	Mean	Std. Deviation	Std. Error Mean		
Creatinine	DM	50	1.44	.90265	.12765	3.125	.002
	Non DM	50	.95	.64370	.09103		
Hb	DM	50	11.85	1.06372	.15043	0.192	.848
	Non DM	50	11.81	1.01887	.14409		
FBS	DM	50	157.50	41.01928	5.80100	9.368	.000
	Non DM	50	100.2800	13.52102	1.91216		
PPBS	DM	50	266.9000	64.35909	9.10175	14.217	.000
	Non DM	50	135.8600	10.29168	1.45546		
HbA1C	DM	50	9.7240	1.90719	.26972	13.684	.000
	Non DM	50	5.9800	.32514	.04598		
Serum Ferritin	DM	50	161.1000	113.55773	16.05949	3.834	.000
	Non DM	50	98.3600	22.22314	3.14283		

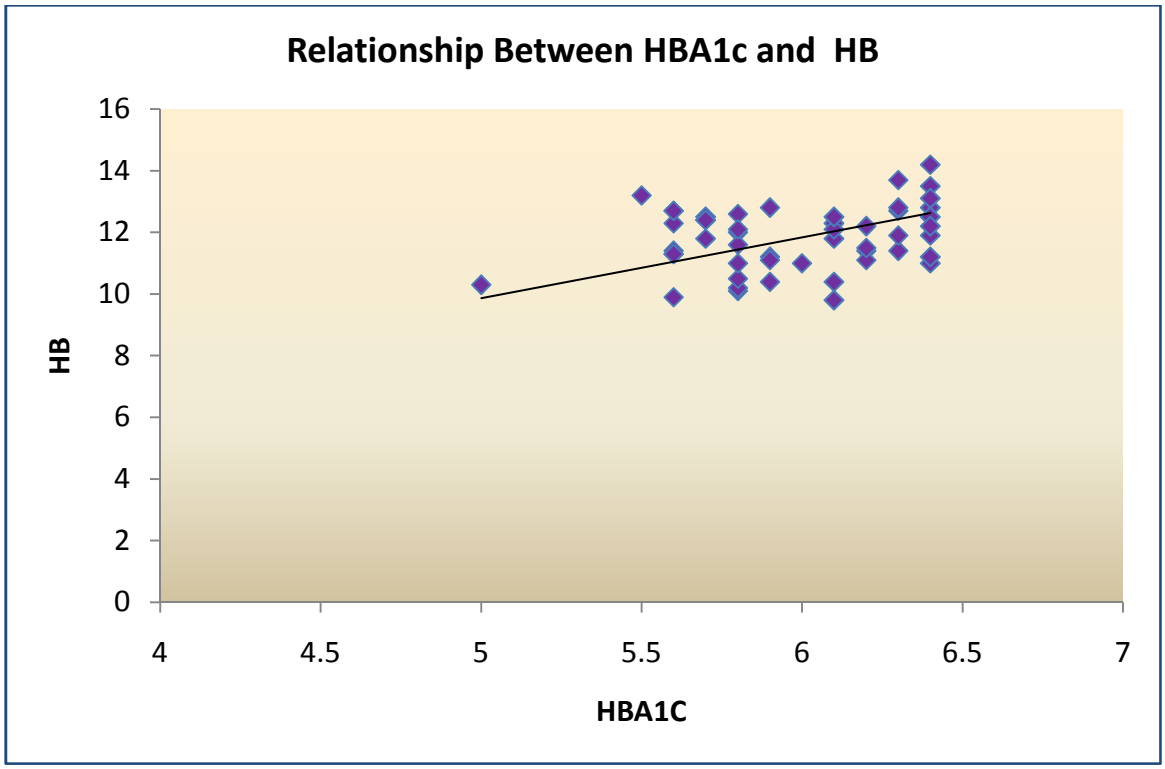

Relationship Between HBA1c and FBS
y = 16.26x
R² = 0.637
FBS
HBA1C
0
50
100
150
200
250
300
0
2
4
6
8
10
12
14
16


Relationship Between HBA1c and PPBS
y = 26.28x
R² = 0.900
PPBs
HBA1C
0
50
100
150
200
250
300
350
400
450
500
0
2
4
6
8
10
12
14
16


Relationship Between FBS and Serum Ferritin
y = 1.083x
R² = 0.403
Serum Ferritin
800
700
600
500
400
300
200
100
0
5
55
105
155
205
255
305
FBS


Relationship Between PPBS and Serum Ferritin
y = 0.616x
R² = 0.207
Serum Ferritin
800
700
600
500
400
300
200
100
0
5
105
205
305
405
505
PPBS


Relationship Between HBA1c and Serum Ferritin
y = 17.04x
R² = 0.203
Serum Ferritin
800
700
600
500
400
300
200
100
0
5
7
9
11
13
15
17
HBA1C


Relationship Between HBA1c and HB
HB
16
14
12
10
8
6
4
2
0
4
4.5
5
5.5
6
6.5
7
HBA1C

For ALL 100 samples

Correlations						
		Hb	**FBS**	**PPBS**	**HbA1C**	**Serum ferritin**
Hb	Pearson Correlation	1	.067	.104	.114	-.067
	Sig. (2-tailed)		.505	.302	.258	.509
	N	100	100	100	100	100
FBS	Pearson Correlation	.067	1	.801**	.805**	.709**
	Sig. (2-tailed)	.505		.000	.000	.000
	N	100	100	100	100	100
PPBS	Pearson Correlation	.104	.801**	1	.975**	.539**
	Sig. (2-tailed)	.302	.000		.000	.000
	N	100	100	100	100	100
HbA1C	Pearson Correlation	.114	.805**	.975**	1	.560**
	Sig. (2-tailed)	.258	.000	.000		.000
	N	100	100	100	100	100
Serum ferritin	Pearson Correlation	-.067	.709**	.539**	.560**	1
	Sig. (2-tailed)	.509	.000	.000	.000	
	N	100	100	100	100	100
**. Correlation is significant at the 0.01 level (2-tailed).						

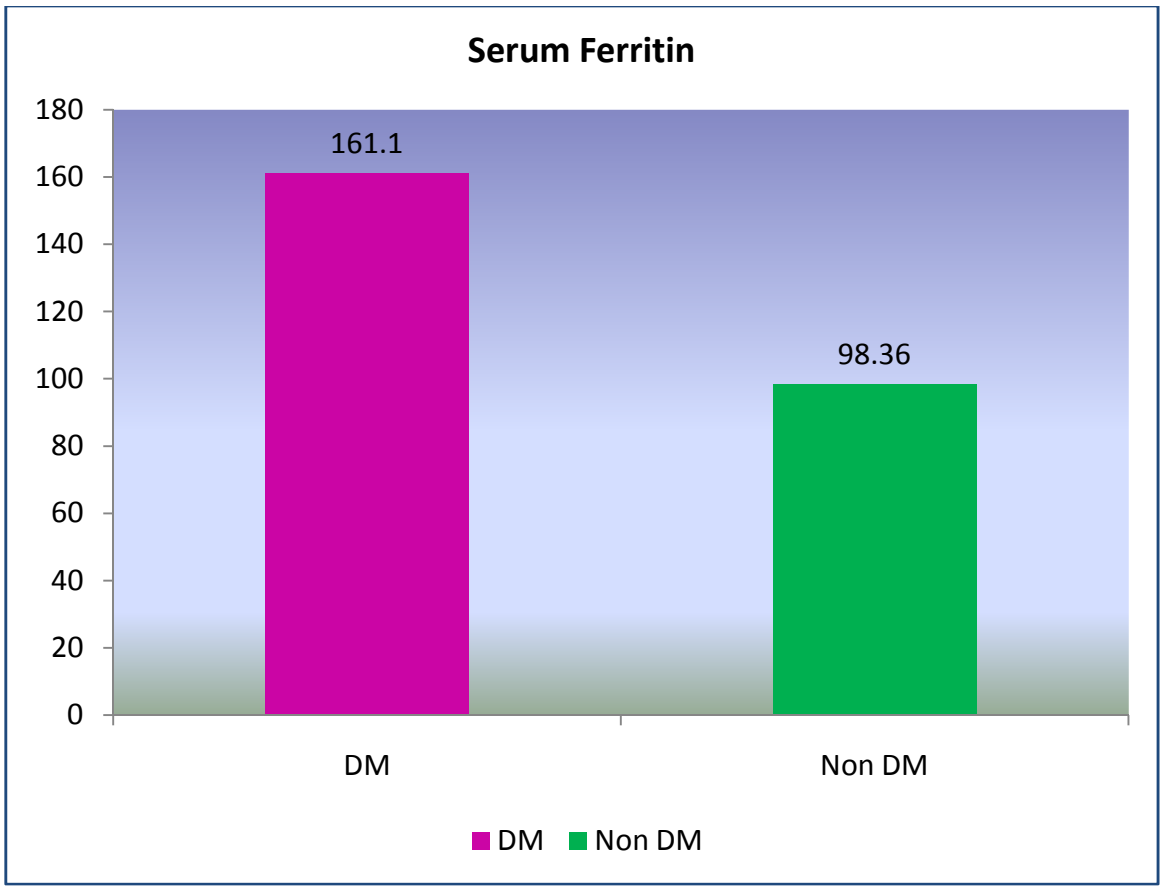
For Non Diabetic

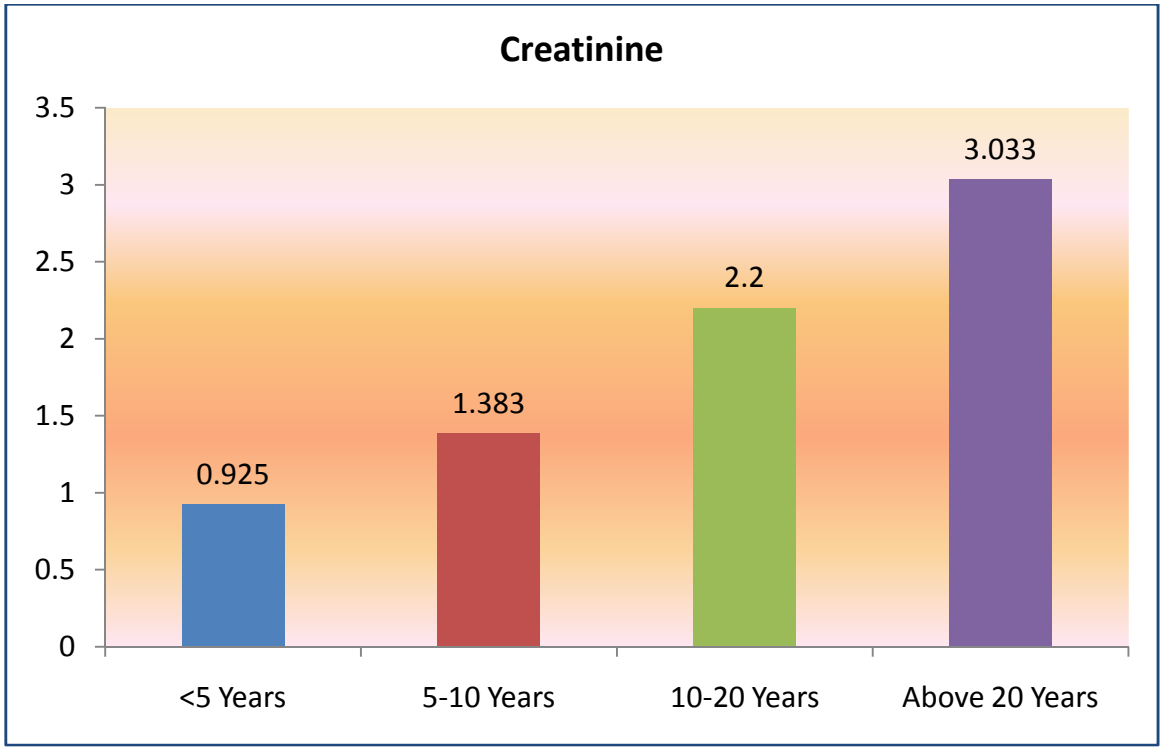
Correlations						
		Hb	**FBS**	**PPBS**	**HbA1C**	**Serum ferritin**
Hb	Pearson Correlation	1	.081	.015	.297*	-.005
	Sig. (2-tailed)		.576	.919	.036	.972
	N	50	50	50	50	50
FBS	Pearson Correlation	.081	1	.197	.123	.143
	Sig. (2-tailed)	.576		.170	.393	.322
	N	50	50	50	50	50
PPBS	Pearson Correlation	.015	.197	1	.273	-.092
	Sig. (2-tailed)	.919	.170		.055	.525
	N	50	50	50	50	50
HbA1C	Pearson Correlation	.297*	.123	.273	1	.146
	Sig. (2-tailed)	.036	.393	.055		.311
	N	50	50	50	50	50
Serum ferritin	Pearson Correlation	-.005	.143	-.092	.146	1
	Sig. (2-tailed)	.972	.322	.525	.311	
	N	50	50	50	50	50

There is no correlation significant at the 0.05 level.

For Diabetic

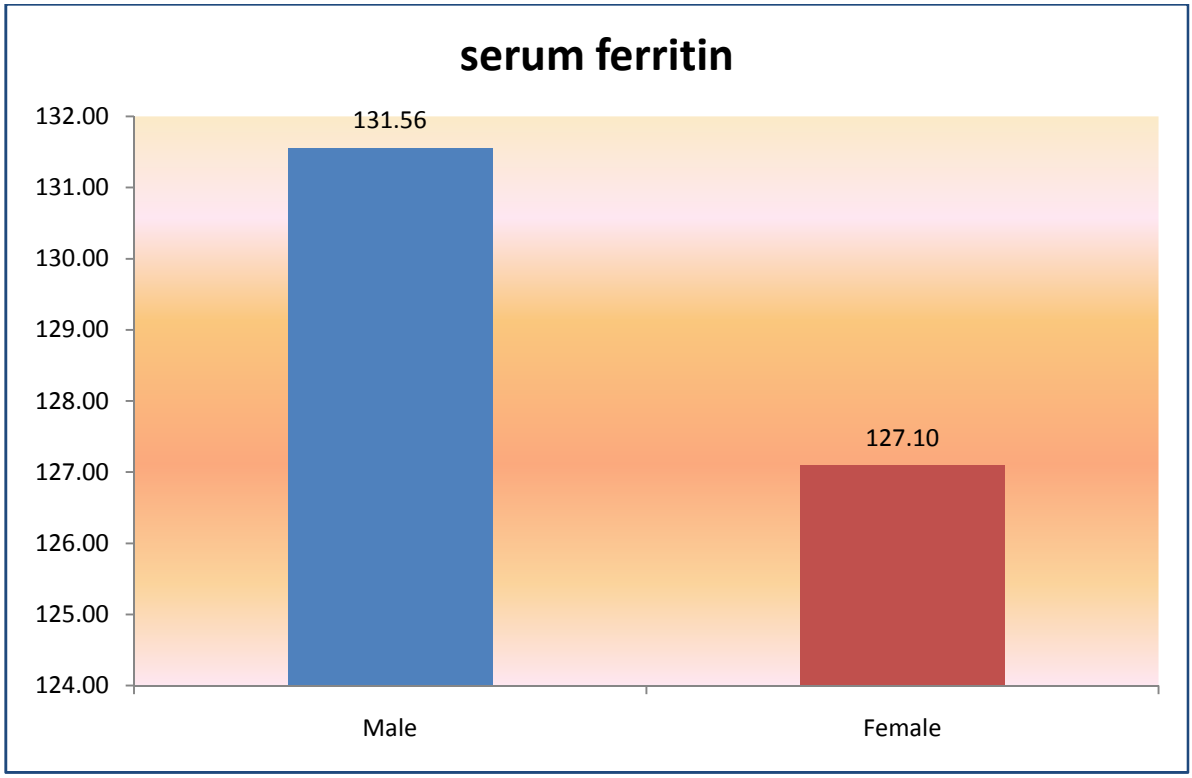
Correlations						
		Hb	**FBS**	**PPBS**	**HbA1C**	**Serum ferritin**
Hb	Pearson Correlation	1	.083	.215	.187	-.111
	Sig. (2-tailed)		.566	.135	.193	.444
	N	50	50	50	50	50
FBS	Pearson Correlation	.083	1	.598**	.615**	.720**
	Sig. (2-tailed)	.566		.000	.000	.000
	N	50	50	50	50	50
PPBS	Pearson Correlation	.215	.598**	1	.942**	.473**
	Sig. (2-tailed)	.135	.000		.000	.001
	N	50	50	50	50	50
HbA1C	Pearson Correlation	.187	.615**	.942**	1	.501**
	Sig. (2-tailed)	.193	.000	.000		.000
	N	50	50	50	50	50
Serum ferritin	Pearson Correlation	-.111	.720**	.473**	.501**	1
	Sig. (2-tailed)	.444	.000	.001	.000	
	N	50	50	50	50	50
**. Correlation is significant at the 0.01 level (2-tailed).						


Serum Ferritin
180
160
140
120
100
80
60
40
20
0
161.1
98.36
DM
Non DM
DM
Non DM


Creatinine
3.5
3
2.5
2
1.5
1
0.5
0
0.925
1.383
2.2
3.033
<5 Years
5-10 Years
10-20 Years
Above 20 Years

Comparison of gender

Independent t test							
Gender		**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**T value**	**P value**
creatinine	Male	59	1.2814	.89220	.11615	1.181	.241
	Female	41	1.0854	.69158	.10801		
Hb	Male	59	11.9932	1.04169	.13562	1.842	.069
	Female	41	11.6098	.99820	.15589		
FBS	Male	59	132.4068	45.02456	5.86170	1.009	.316
	Female	41	123.8293	36.70824	5.73286		
PPBS	Male	59	203.3051	75.90199	9.88160	0.286	.775
	Female	41	198.6098	87.00025	13.58716		
HbA1C	Male	59	7.8915	2.21696	.28862	0.203	.839
	Female	41	7.7951	2.49278	.38931		
Serum ferritin	Male	59	131.5593	74.50510	9.69974	0.250	.803
	Female	41	127.0976	103.92781	16.23080		



Comparison of Duration of DM

		N	Mean	S.D	S.E	95% Confidence Interval for Mean		Minimum	Maximum	F value	P value
						L.B	U.B				
Creatinine	<5 Years	20	.925	.572	.128	.657	1.19	.925	.57	12.81**	.000
	5-10 Years	18	1.38	.677	.160	1.04	1.72	1.38	.67		
	10-20 Years	9	2.20	.971	.324	1.45	2.94	2.20	.97		
	Above 20 Years	3	3.03	.321	.186	2.23	3.83	3.03	.32		
	Total	50	1.44	.903	.128	1.18	1.70	1.44	.90		
Hb	<5 Years	20	11.97	1.095	.245	11.45	12.48	11.97	1.09	.184	.907
	5-10 Years	18	11.72	.751	.177	11.35	12.10	11.72	.75		

	10-20 Years	9	11.91	1.504	.501	10.75	13.06	11.91	1.50		
	Above 20 Years	3	11.70	1.473	.850	8.04	15.35	11.70	1.47		
	Total	50	11.856	1.064	.150	11.554	12.15	11.85	1.06		
FBS	<5 Years	20	153.75	43.99	9.83	133.16	174.34	153.75	43.99	.399	.754
	5-10 Years	18	155.00	34.15	8.05	138.01	171.98	155.00	34.15		
	10-20 Years	9	171.22	51.08	17.02	131.95	210.48	171.22	51.08		
	Above 20 Years	3	156.33	37.89	21.88	62.18	250.48	156.33	37.89		
	Total	50	157.50	41.01	5.80	145.84	169.15	157.50	41.01		
PPBS	<5 Years	20	264.30	65.42	14.63	233.67	294.92	264.30	65.42	.115	.951
	5-10 Years	18	267.88	57.08	13.45	239.50	296.27	267.88	57.08		
	10-20 Years	9	275.66	85.60	28.53	209.86	341.46	275.66	85.60		
	Above 20 Years	3	252.00	55.24	31.89	114.76	389.23	252.00	55.24		
	Total	50	266.90	64.35	9.10	248.60	285.19	266.90	64.35		
HbA1C	<5 Years	20	9.49	1.75	.392	8.67	10.31	9.49	1.75	.250	.861
	5-10 Years	18	9.88	1.88	.444	8.95	10.82	9.88	1.88		
	10-20 Years	9	10.03	2.50	.834	8.10	11.95	10.03	2.50		
	Above 20 Years	3	9.33	1.80	1.04	4.85	13.81	9.33	1.80		
	Total	50	9.72	1.90	.270	9.18	10.26	9.72	1.90		

Serum ferritin	<5 Years	20	146.80	77.51	17.33	110.52	183.07	146.80	77.51	1.357	.268
	5-10 Years	18	143.72	91.53	21.57	98.20	189.24	143.72	91.53		
	10-20 Years	9	229.22	197.60	65.87	77.32	381.11	229.22	197.60		
	Above 20 Years	3	156.33	75.92	43.83	-32.27	344.93	156.33	75.92		
	Total	50	161.10	113.55	16.05	128.82	193.37	161.10	113.55		

** Correlation is significant at p<0.01

DISCUSSION

DISCUSSION

- A total of 100 participants took part in this study of which 50 were cases, that is diabetics and the others were controls or non-diabetics. Of the total study population 35% belonged to the age group of 61-70 years, 25% belonged to the age group of 51-60 years and 24% belonged to the 71-80 years age group. 10% of them were above 81 years of age whereas only 6% were below 50 years of age. Similarly 59 of the total participants were males and the remaining 41 females. On a comparison study between the age group employed in both the cases and controls, the p value was found to be 0.190 thereby making age an insignificant factor, or removing it from the list of confounding factors. **There is no statistically significant difference in age distribution in cases and controls.**

- On comparing the proportion of males and females in the cases and controls, it is seen that the p value is 0.542, clarifying that the cases and controls have been gender-matched appropriately. Nearly 38% of diabetics and 44% of non-diabetics are females. In total, 59% of the study participants are males and 41% are females. **There is no statistically significant difference in sex distribution in cases and controls.**

- Both the cases and the controls had their equal share of Comorbidities, thereby removing it from the list of confounding factors. Around 8 cases had hypertension as compared to 11 controls. 12 out of 50 cases had associated coronary artery disease as compared to 12 out of 50 controls. Nearly 50% of

the participants from both the cases as well as the controls had underlying Comorbidities. **There is no statistically significant difference in the distribution of comorbidities in cases and controls.**

- On a comparison between the two groups for the various values obtained during the study, the following parameters such as creatinine, fasting blood sugar, post-prandial blood sugar, HbA1C, and serum ferritin levels were found to be significantly different. The mean creatinine in diabetics was 1.44 compared to 0.95 in non-diabetics. With a p value of 0.002 this would be deemed significant.

- On the other hand, the mean haemoglobin levels between the two groups were not significant with a value of 11.85 in one and 11.81 in the other, and the p value being 0.848. **There is no statistically significant difference in haemoglobin values and their distribution in cases and controls.**

- The mean fasting blood glucose value in diabetics was 157.5 whereas it was 100.7 in the non diabetics. The p value was in the order of 0.000? and hence termed significant. The mean post-prandial glucose levels were 266.9 in the diabetics and 135.8 in the non-diabetics and the p value was significant for <0.001. Hence this association is also branded significant.

- The HbA1C was 9.72 among the diabetics and 5.98 among the controls. P value was less than 0.001.

- In the first chart comparing the various values of non-diabetics or the control group it is seen that there is a correlation between haemoglobin and HbA1C levels as $p<0.05$ ($p=0.036$). The association between haemoglobin and HbA1C levels is therefore significant in the control group. But even after a thorough analysis, there was no further association between the other parameters such as FBS, PPBS, HbA1C and serum ferritin. **There is no statistically significant association between the blood glucose parameters and serum ferritin levels among controls.**

- Of a total of 50 cases of diabetics, nearly 32 had serum ferritin levels above 100 showing that the prevalence of elevated serum ferritin in type 2 diabetics is around 64% in this study. The same could not be told about non diabetics where only 18 of the 50 had ferritin above 100, giving a mere prevalence of 36%. The p value was less than the order of 0.001 while comparing the fasting blood glucose and the serum ferritin values in diabetics thereby making the association significant. **Hence serum ferritin levels are directly proportional to fasting blood glucose values in diabetics.**

- The p value was found to be 0.001 for the study of association between post-prandial blood sugar levels and serum ferritin thereby making the association significant. **Hence, serum ferritin values are also directly proportional to the post- prandial blood glucose values in diabetics.**

- On a comparison between the HbA1C levels and serum ferritin levels in diabetics, the p value was less than 0.001 and hence the association was

significant at the 0.01 level and showed that both parameters correlated with each other. **Hence serum ferritin levels were also found to be directly proportional to HbA1C levels among diabetics.**

- Most importantly, the mean serum ferritin in diabetics was 161.1 whereas in non-diabetics it was 98.36 with a p value < 0.001 making it statistically significant. **Thus diabetes is associated with elevated serum ferritin levels.**

- The duration of diabetes in individuals did not have a significant correlation with any of the above parameters except serum creatinine levels. The mean serum creatinine was 0.92 in those with less than 5 years of diabetes and 3.03 in those with more than 20 years of diabetes. **Therefore increased duration of diabetes is associated with rising serum creatinine levels.**

- The duration of diabetes and serum ferritin levels were compared between the participants and the p value was found to be >0.05, thereby making the association insignificant. **Hence it is seen that the duration of diabetes is not associated with serum ferritin levels.**

- The duration of diabetes and fasting and post-prandial blood glucose values were not found to correlate with each other. The p values were greater than 0.01, thereby making it clear that **the duration of diabetes is not associated with rising blood glucose values.**

All the participated diabetics of this study were further followed up for adequate management and treated with appropriate drugs according to the ADA guidelines.

CONCLUSION

CONCLUSION

Many studies have demonstrated the relationship between serum ferritin levels and diabetes mellitus so much so that an entity called high ferritin diabetes itself has been coined in the recent times. In this study, there is a positive correlation between type 2 diabetes mellitus and serum ferritin levels and the various markers of diabetes as well. Serum ferritin has also been shown to correlate with the other markers for diabetes such as fasting and post-prandial blood glucose levels, that is higher the values of fasting or post prandial blood glucose levels higher is the serum ferritin in such patients. The study also shows that the correlation between fasting blood glucose and serum ferritin is slightly higher than that of post-prandial glucose levels and serum ferritin. The prospective of serum ferritin as a diabetes marker has also been explored and shows positive results.

LIMITATIONS OF THE STUDY

LIMITATIONS OF STUDY

- The major limitation of the study includes its relatively small sample size which precludes us from getting the statistical significance with respect to certain variables such as creatinine, which could be a confounding factor.

- The effects of iron supplementation have not been included in this study which could have led to clearer concepts about the frequent over the counter use of drugs in diabetics and how it would impact them.

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ANNEXURES

PROFORMA

Patient profile

NAME: OP/IP NO:

AGE: DOA:

SEX: DOD:

OCCUPATION:

ADDRESS:

PRESENTING COMPLAINTS

Duration of current complaint:

Any active infection at present:

History of steroid use at present:

History of blood transfusions:

PAST HISTORY

Diabetes mellitus-

HTN –

Renal insufficiency-

Liver disease-

H/O vascular events-

Hypothyroidism-

Coronary artery disease-

PERSONAL HISTORY

Appetite-

Diet-

Sleep-

Smoking –

Alcohol intake-

GENERAL PHYSICAL EXAMINATION

Built – poor/moderate/well

Nourishment – poor/moderate/well

Pallor-

Icterus-

Cyanosis

Clubbing-

Lymphadenopathy-

Edema-

Weight-

Height-

VITALS

Pulse-

B.P-

Temperature-

SYSTEMIC EXAMINATION

CVS-

RS-

P/A-

CNS-

INVESTIGATIONS

1. RFT :
2. LFT :
3. FBS :
4. PPBS :
5. U/R :
6. HbA1C :
7. SERUM FERRITIN:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr. S. SRIVIDHYA
I Yr. PG in MD GENERAL MEDICINE
INSTITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI

Dear Dr. S. SRIVIDHYA,

The Institutional Ethics Committee has considered your request and approved your study titled **"A CASE CONTROL STUDY ON THE RELATIONSHIP BETWEEN SERUM FERRITIN LEVELS AND TYPE 2 DIABETES MELLITUS AND ITS PROSPECTS AS A DIABETES CONTROL INDEX" - NO.20032018**

The following members of Ethics Committee were present in the meeting held on **27.03.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. S. Purushothaman, Associate Professor of Pharmacology, MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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Instances where selected sources appear:

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CERTIFICATE-II

This is to certify that this dissertation work titled "**A CASE CONTROL STUDY ON THE RELATIONSHIP BETWEEN SERUM FERRITIN LEVELS AND TYPE 2 DIABETES MELLITUS AND ITS PROSPECTS AS A DIABETES CONTROL INDEX**" of the candidate **Dr.S.SRIVIDHYA** with registration number **201711018** for the award of M.D., in the branch of general medicine. I personally verified the urkund.com website for plagiarism check. I found that the uploaded file contains pages from introduction to conclusion and the result shows **1 percentage of plagiarism** in the dissertation.

Guide and supervisor sign with seal

INFORMATION TO PARTICIPANTS

INVESTIGATORS: Dr.S.SRIVIDHYA

Dr.R.MUTHUSELVAN M.D.,

NAME OF THE PARTICIPANT:

You are invited to take part in this study. The information in this document is to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

We are conducting a case control study on the relationship between serum ferritin levels and type 2 diabetes mellitus and its prospects as a diabetes control index among patients attending the Rajiv Gandhi Government General Hospital, Chennai. Your cooperation to undergo relevant investigations as per need may be of an immense value to us. The purpose of this study is to find the association between serum ferritin and type 2 diabetes.

We are selecting certain cases and if you are found eligible we would like to perform some tests and you will be subjected to a blood investigation which in no way will affect your final result or the management of your current condition.

The privacy of the patients participating will be maintained throughout the study. In the event of any publication or presentation resulting from the research no personal information of the patients shall be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or withdraw at any time and your decision will not result in any loss of benefits to which you are already entitled.

If anything is found abnormal, the results of the study may be informed to you at the end of the study or during the study period which will only aid in your further management.

Signature of investigator Signature of participant

Date:

Place:

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு : **நீரிழிவு நோயில் சீரம் ஃபெரிட்டின் அளவுகளில் ஏற்படும் மாற்றங்களை கணக்கிடுதல் பற்றிய ஆய்வு.**

ஆய்வாளர் பெயர் : **மரு. S. ஸ்ரீவித்யா**

ஆய்வு நிலையம் : பொது மருத்துவப் பிரிவு,
சென்னை மருத்துவக் கல்லூரி, சென்னை-3.

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலாமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

இதில் நீரிழிவு நோயில் சீரம் ஃபெரிட்டின் அளவுகளில் ஏற்படும் மாற்றங்களை கணக்கிடுதல் பற்றிய ஆய்வு நடைபெறுகிறது. அதற்கு இரத்தப் பரிசோதனை அவசியம், அதற்குத் தங்கள் ஒத்துழைப்புத் தேவை.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனையின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

தேதி :

பங்கேற்பாளர் கையொப்பம் /
இடது கட்டைவிரல் ரேகை

தேதி :

PATIENT CONSENT FORM

Study detail : **A CASE CONTROL STUDY ON THE RELATIONSHIP BETWEEN SERUM FERRITIN AND TYPE 2 DIABETES MELLITUS AND ITS PROSPECTS AS A DIABETES CONTROL INDEX.**

Study centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's name :

Patient's age :

Identification No:

Documentation of the informed consent

1. I_____ have read the information in this form. I was free to ask any questions and they have been answered. I am over 18 years of age and I am exercising my free power of choice and I hereby give consent to be a participant in this study.

2. I have read and understood this consent form and the information provided to me.

3. I have had the consent document explained to me.

4. I have been told about the nature of the study.

5. I have been informed about my rights and responsibilities by the investigator.

6. I am aware of the fact that I can opt out of the study at any time without having to give any reason and that will not affect my future course of treatment in this hospital.

7. I hereby give permission to the investigators to release the information obtained from my participation to the sponsors, regulatory authorities, government agencies, and IEC. I understand that they are publicly published.

8. I have understood that my identity will be kept confidential if the data are presented in public.

9. I have had all my questions answered to my satisfaction.

10. I have decided to be in the research study.

11. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

Name and signature/thumb impression of the participant/impartial witness

_____	_____	_____
NAME	SIGNATURE	DATE

Name and signature of impartial witness required for illiterate patients:

_____	_____	_____
NAME	SIGNATURE	DATE

Address and contact no of the impartial witness:

Name and signature of the investigator:

_____	_____	_____

ஆய்வு ஒப்புதல் படிவம்

ஆய்வு தலைப்பு : **நீரிழிவு நோயில் சீரம் ஃபெரிட்டின் அளவுகளில் ஏற்படும் மாற்றங்களை கணக்கிடுதல் பற்றிய ஆய்வு.**

பெயர் :
வயது :
பால் :

தேதி :
வெளிநோயாளி எண் :
ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் நீரிழிவு நோயில் சீரம் ஃபெரிட்டின் அளவுகளில் ஏற்படும் மாற்றங்களை கணக்கிடுதல் பற்றிய ஆய்வு நடைபெறுகிறது என்பதை ஆராய்ச்சியாளர் கூற அறிந்துகொண்டேன்.

மேற்கண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

நான் ஆராய்ச்சியாளருடன் ஒத்துழைப்பேன் என்றும், எனக்கு ஏற்படக்கூடிய ஆசாதாரண நிகழ்வுகள் பற்றியும் உடனடியாக ஆராய்ச்சியாளரிடம் தெரிவிப்பேன் என்று உறுதி கூறுகிறேன். இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் எக்காரணமும் கூறாமல் என்னை விடுவித்துக்கொள்ளலாம் என்பதை அறிவேன்.

என்னிடம் இருந்து பெறப்படும் தகவல்களை அரசு, வரைமுறை அதிகாரிகள் ஆகியோர்களுடன் பகிர்ந்துகொள்ள ஆராய்ச்சியாளருக்கு அனுமதி அளிக்கிறேன். என்னுடைய சிகிச்சைக்கட்டுகளை பார்வையிட உரிமை உண்டு. என்னுடைய தகவல்களின் அடையாளம் இரகசியமாக வைக்கப்படும் என்பதை அறிவேன்.

இந்த ஆராய்ச்சியில் பங்கேற்க தன்னிச்சையாக முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் / ரேகை

பங்கேற்பவர் பெயர்

இடம் :

தேதி :

ஆய்வாளர் கையொப்பம்

ஆய்வாளர் பெயர்

இடம் :

தேதி :

CASES										
S.No.	Age	Gender	Duration	Comorbidities	Creatinine	Hb	FBS	PPBS	HbA1C	Serum Ferritin
1	47	female	1 year	none	0.9	12.7	114	256	9	145
2	54	male	2.5 years	none	0.7	13.1	122	243	8.7	79
3	65	male	10 years	hypertension	0.9	12.4	154	211	7.3	90
4	56	male	2 years	hypertension	0.7	13	188	314	11.5	234
5	53	male	8 years	cad	0.9	12.1	210	354	12.6	455
6	62	female	3 years	hypertension	1.1	12.9	124	192	7.9	89
7	66	female	0.5 years	cad	0.5	11	180	244	9.7	188
8	68	male	1.5 years	none	0.4	11.1	129	212	8.2	97
9	84	male	19 years	nephropathy	2.7	13.6	267	319	12.5	376
10	77	male	17 years	cad,nephropathy	2.3	11.6	143	289	10.9	199
11	73	female	12 years	nephropathy	3.1	14.3	171	458	14.6	155
12	76	male	6 years	none	1.1	12.9	116	189	7.4	65
13	79	male	23 years	nephropathy	2.9	13	137	258	9.2	112
14	82	male	9 years	cad,nephropathy	3.7	10.6	190	276	10	174
15	54	female	4 years	hypertension	1.6	11.1	254	398	12.5	322
16	61	female	5.5 years	cad,hypertension	1.3	12.1	129	357	13.8	101
17	63	female	2.5 years	none	0.6	10.8	110	199	7.5	68
18	78	male	8 years	cad,nephropathy	2.2	10.5	129	180	8.6	97
19	68	female	5 years	none	0.7	12.4	142	259	9.4	115
20	76	male	25 years	nephropathy	3.4	12	132	194	7.6	113
21	64	male	6 years	none	1.5	11.3	122	298	10.8	90
22	75	female	4 years	none	1	11.3	100	222	8.9	98
23	50	male	1 year	cad	1	14.6	137	257	9	122
24	63	male	8 years	none	1.4	11.8	152	277	8.3	132
25	71	female	7.5 years	hypothyroidism	1.6	11.9	145	251	8.9	135
26	70	female	6 years	cad,hypertension	1.1	12.7	144	230	9.4	95
27	63	male	0.5 years	none	0.4	12.4	163	253	8.7	129
28	60	female	1.5 years	none	0.6	11.1	121	216	7.9	77

S.No.	Age	Gender	Duration	Comorbidities	Creatinine	Hb	FBS	PPBS	HbA1C	Serum Ferritin
29	82	male	15 years	cad	0.8	13	111	199	7.8	64
30	81	male	21 years	nephropathy	2.8	10.1	200	304	11.2	244
31	57	male	6 years	none	0.9	12.1	188	316	11.1	1265
32	74	female	17 years	nephropathy	3.5	10.1	211	294	10.5	695
33	81	male	13 years	alzheimers	1.4	11.2	138	198	7.6	115
34	66	female	14 years	none	1.8	11.1	126	211	8	97
35	64	male	3.5 years	hypertension	1.6	12.8	234	269	9.4	269
36	71	male	5 years	nephropathy	2.9	12.3	118	214	8.1	112
37	76	female	8 years	none	1.5	11.1	155	282	9.8	121
38	54	male	4 years	none	0.7	12.4	212	299	11.3	211
39	63	female	1.5 years	none	0.6	10.5	164	404	13.7	2784
40	66	male	2 years	none	0.9	10.3	118	177	7.1	77
41	65	female	7 years	none	0.9	11.3	127	231	9.4	88
42	68	male	10 years	cad	1.2	10.8	109	239	7.9	111
43	78	male	18 years	cad,nephropathy	3.1	10	155	201	7.5	131
44	77	male	12 years	none	1.1	12.3	219	312	10.9	231
45	67	male	3 years	none	1	12.4	148	375	11.4	70
46	63	female	2.5 years	none	0.6	11.2	197	283	10	156
47	73	female	5.5 years	cad,hypertension	1	11.1	127	180	7.9	95
48	75	male	7.5 years	alzheimers	1.6	11.3	173	312	11.4	119
49	64	male	9 years	none	1.3	12.7	199	333	11.6	150

CONTROLS

S.No.	Age	Gender	Duration	Comorbidities	Creatinine	Hb	FBS	PPBS	HbA1C	Serum Ferritin
1	65	male	-	hypertension	0.9	13.7	100	139	6.3	100
2	73	female	-	hypertension	0.7	11	99	128	6	97
3	45	female	-	none	0.6	10.3	93	140	5	75
4	81	male	-	old CVA	0.9	12.3	102	124	6.1	103
5	62	female	-	none	1.1	12	105	123	5.8	78
6	55	male	-	none	0.4	13.2	98	126	5.5	89
7	68	male	-	none	0.6	11.3	87	128	5.6	94
8	51	male	-	none	0.7	11.4	109	129	6.2	104
9	59	female	-	none	0.7	11.1	106	132	6.2	100
10	66	male	-	hypertension, cad	1.1	14.2	118	130	6.4	94
11	44	male	-	none	0.8	11.8	73	121	6.1	76
12	71	male	-	hypertension, old CVA	0.6	12.1	101	146	6.1	66
13	85	female	-	ckd	2.6	10.1	119	128	5.8	84
14	53	male	-	none	0.9	12.4	88	125	5.7	88
15	55	male	-	cad, hypertension	0.6	11.4	85	133	5.6	86
16	56	female	-	none	0.8	11.4	104	143	6.3	108
17	64	male	-	seizure disorder	0.8	11.6	92	125	5.8	154
18	62	female	-	none	0.6	12.3	95	125	5.6	75
19	69	female	-	old CVA	0.5	12.5	95	128	5.7	105
20	71	male	-	none	0.5	12.7	128	149	5.6	95
21	77	female	-	none	0.8	12.7	115	135	6.3	102
22	49	male	-	none	0.7	11.9	102	137	6.4	77
23	56	female	-	none	0.7	12.8	103	139	6.3	69
24	55	male	-	none	0.7	12.6	102	132	5.8	83
25	59	female	-	none	0.6	12.8	105	141	5.9	97
26	64	male	-	ckd	3.9	9.9	92	148	5.6	95
27	67	female	-	none	0.9	11.5	83	125	6.2	100
28	76	male	-	old CVA	0.8	12.8	87	128	6.4	104

S.No.	Age	Gender	Duration	Comorbidities	Creatinine	Hb	FBS	PPBS	HbA1C	Serum Ferritin
29	77	female	-	cad	1	12.5	90	162	6.1	88
30	83	male	-	hypertension, cad	0.6	11.9	99	133	6.3	173
31	48	female	-	none	1	12.7	110	126	5.6	134
32	52	male	-	none	0.8	12.4	126	140	5.7	97
33	63	male	-	none	1	12.5	134	155	6.4	112
34	66	female	-	ckd,hypertension	2.4	10.2	88	132	5.8	139
35	58	female	-	none	0.7	13.5	81	152	6.4	77
36	57	male	-	none	0.5	12.2	92	138	6.2	89
37	69	male	-	cad	0.6	13.1	106	132	6.4	166
38	57	female	-	none	0.8	10.4	106	131	6.1	103
39	64	male	-	cad,ckd,hypertension	2.9	9.8	103	131	6.1	102
40	53	male	-	none	0.9	11	104	155	6.4	99
41	85	male	-	cad	0.7	11.2	92	140	5.9	94
42	75	female	-	none	1	10.4	91	139	5.9	92
43	72	male	-	hypertension, old CVA	1.1	10.5	103	148	5.8	111
44	65	female	-	none	0.8	11.2	105	143	6.4	69
45	62	male	-	none	1.2	11.3	88	133	5.6	87
46	76	female	-	none	0.9	11.8	95	134	5.7	101
47	83	male	-	old CVA,hypertension	1.2	12.2	96	166	6.4	108
48	55	male	-	hypertension	0.9	12.1	71	126	5.8	79
49	52	female	-	none	0.6	11	119	136	5.8	99
50	54	female	-	none	0.7	11.1	129	134	5.9	101