Incorporating patient blood pressure levels into daily insulin dosing regimens

A project submitted

by

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Dedicated to my beloved family and respected teachers who supported and guided me through thick and thin and assisted me to achieve my goals.

Certification Statement

This is to certify that the project titled “Incorporating patient blood pressure levels into daily insulin dosing regimens” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Rubayat Islam Khan, Senior lecturer, Department of Pharmacy, BRAC University that appropriate credit is given where I have used the language, ideas or writings of another.

Signed

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Countersigned by the Supervisor

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Abstract

There has been an expansion in the commonness of diabetes mellitus in the course of recent years. There has also been additionally extensive confirmation for an expanded predominance of hypertension in diabetic people. Both hypertension and diabetes that have inclined to the improvement of cardiovascular diseases (CVD) and renal disease. Subjects having diabetes are at around 60% expanded danger of early mortality. The nearness of hypertension in diabetic patients considerably has built and enhance the dangers of coronary heart disease, stroke, nephropathy and retinopathy. Epidemiologic examinations which give confirmation to concurrence of hypertension and diabetes and perhaps point towards a typical hereditary and natural factor advancing both diabetes and hypertension. The connection amongst diabetes and hypertension get fueled by 2 particular observations where the one that was nonattendance of successful antihypertensive medications but this has been changed because new medications have been produced for the better care of the patient and the other one which was the insulin resistance that is currently one of the main considerations adding to hypertension. The basic pathways by which diabetes and hypertension often happen together is incorporated by- obesity, inflammation, oxidative stress and insulin resistance. Insulin resistance, expanded tissue inflammation and reactive oxygen species (ROS) generation that brings about endothelial dysfunction, expanded tissue renin-angiotensin-aldosterone framework (RAAS) and expanded sympathetic nervous system (SNS) action have all been involving in this complex pathophysiology of diabetes and hypertension. Again, the reason for high blood pressure with diabetes is because high blood sugar levels damage the blood vessels and cause cholesterol abnormalities which is common for people with type 2 diabetes. Type 2 diabetes causes high blood pressure because high insulin levels stimulate the nervous system which then speeds up the heart and makes blood vessels narrower causing blood pressure to increase arteries carry blood from heart and it is the force of the blood pushing against the artery walls. The damage caused from this force on artery walls can cause them to get more narrow and the end result of this is heart attack or stroke. The aim of this study is to adjust the total daily insulin dosage for the patients who are already on an insulin treatment regimen by using a fuzzy-based system.

Chapter 1: Introduction

The relationship amongst insulin and high blood pressure has been broadly investigated in the midst of the earlier decade and continued to be a region of extreme debate as well as discussion. Enthusiasm for the connection amongst insulin and hypertension was powered by two distinctive perceptions: (i) lack of proper antihypertensive medications for decreasing the expanded danger of heart diseases in hypertensive patients and [Collins et al, 1990; Komer et al, 1982; Wikstrand et al, 1988 and MacMahon et al, 1989]. (ii) the acknowledgment that fundamental hypertension is commonly associated with insulin resistance and hyperinsulinemia [Ferrannini et al, 1991 and Reaven, 1991] .These two perceptions prompted the supposed "insulin hypothesis" of high blood pressure where it was hypothesized that insulin resistance or potentially hyperinsulinemia might be casually related to the improvement of this hypertension [Reaven, 1988 and DeFronzo, 1992].

Subsequent examinations revealed that deformations in glucose metabolism are connected with [Reaven, 1991; DeFronzo, 1991; Kannell, 1991; Sowers et al, 1991; Weidmann et al, 1993and Haffner, 1992]. Recent reports obviously demonstrate that insulin resistance and hyperinsulinemia are accessible in normotensive offsprings of patients with high blood pressure as in front of timetable as the second decade of life and that these progressions precede the ascent in blood pressure(BP) mostly [Allemann et al, 1995 and Grunfeld et al, 1994]. The perception that insulin resiatence and hyperinsulinemia happen in untreated human hypertensives [Ferrannini et al, 1987 and Shen et al, 1988] sometimes accompanying in a few rodent models of hypertension [Reaven, 1991; Kotchen et al, 1991 and Mondon et al, 1988] fortifies the conflict that these variations from the norm are characteristically connecting with hypertension and are not considered to be insignificant incidental discoveries. Researches demonstrate that hyperinsulinemia is an independent risk factor for this coronary artery disease that can be life threatening sometimes [Ducimetiere et al, 1980 and Pyorala et al, 1979] and that even a little level of glucose intolerance can suddenly increase the danger of creating such disease [Fuller et al, 1991].

DeFronzo et al. were the first ones showing direct sodium- retaining effect of insulin in healthy subjects. They performed euglycemic insulin clamps in youthful subjects and surprisingly found that urinary sodium excretion level goes down within 30-60 minutes of a physiological increment in plasma insulin concentration and step by step achieved a

minimum level, which was 50% or half lower than the basal rate. This perception by this manner affirmed in various subjects including humans [Gans et al, 1991], dogs [DeFronzo et al, 1976] and rats respectively [Kirchner, 1988]. The hypothesis that hyperinsulinemia prompts renal sodium and liquid maintenance is in perspective of the doubt that the kidneys of hypertensive patients keep up standard affectability to the antinatriuretic effect of insulin, as opposed to the fringe tissues which are impervious to insulin's glucoregulatory impacts. This present has been particularly avowed in essential hypertensive subjects, where it was displayed that notwithstanding the way that insulin-mediated glucose take-up was remarkably lower in hypertensives, insulin-affected sodium upkeep was kept up when appeared differently in relation to normotensive controls [Shimamoto et al, 1994]. Similarly, it was starting late point by point that in hypertensive patients, insulin particularly extended sodium reabsorption in the proximal and distal tubules [Endre et al, 1994 and Kageyama et al, 1994].

These reports raising the likelihood that insulin might cause sodium and volume over-load in hypertensive subjects particularly, which could prompt hypertension. An ongoing examination showed out that in spite of the fact that the sodium-retaining impact of insulin was being kept up in hypertensive patients, they were impervious to the – natriuretic impacts of atrial natriuretic peptide [Abouchacra et al, 1994].As a result, this novel discovering raises the likelihood that protection from the natriuretic impacts of atrial natriuretic peptide might be one of the instruments fundamental the insulin-initiated increment in blood pressure of an individual.

Decreased tissue sensitivity to insulin is a normal for different obsessive conditions named the insulin resistance syndrome, otherwise called the metabolic syndrome or cardiometabolic disorder [Schulman, 2009]. The metabolic syndrome is definitely not a solitary ailment, yet rather is a complex clustering of bunch of indications that incorporate- a large abdomen periphery, hypertension, hyperglycemia, dyslipidemia and insulin resistance, which are all normally thought to be connected with expanded danger of the obesity and Type 2 Diabetes [Khoshdel et al, 2012]. As patients with ‘metabolic syndrome’ are ordinarily burdened with- cardiovascular morbidities, the metabolic syndrome and cardiovascular ailments share common pathways including expanded oxidative stress, flawed glucose, lipid metabolism, low grade inflammation, hypercoagulability and endothelial damage. Beforehand, examiners suggested for utilizing the "circulatory syndrome" to refine the metabolic syndrome idea through the expansion of markers of cardiovascular diseases, for example- renal impairment,

microalbuminuria, arterial stiffness and left ventricular dysfunction. It is now clear that insulin obstruction and the endeavors made by the insulin-focused on organs to make up for this deformity and assume an indispensable part in the pathogenesis and clinical course of the metabolic syndrome [Ginsberg, 2000].

Insulin resistance and hypertension are the components of metabolic syndrome and are existing regularly together [Zhou et al, 2012]. Clinical examinations have demonstrated that around half of hypertensive people have hyperinsulinemia (or glucose intolerance), though up to 80% of patients along with type 2 diabetes seen to have hypertension [Zhou et al, 2012; Lastra et al, 2010]. Notwithstanding its metabolic impacts, insulin incites vasorelaxation by a stimulation in the creation of nitric oxide (NO) in endothelium [Scherrer et al, 1994] and manages sodium homeostasis by upgrading sodium reabsorption in the kidney [Manhiani et al, 2011; Horita et al, 2011]; in this manner, adding to the control of blood pressure. Ongoing examinations have shown that insulin resistance can create in the great insulin-responsive tissues, as well as in cardiovascular tissues where insulin takes an interest in improving cardiovascular illnesses and hypertension [Schulman, 2009; Cooper et al, 2007]. Insulin resistance slowly picked up a terrible name and is now seen as deleterious: generally connected with the metabolic syndrome and hypertension that unwantedly present an expanded hazard for type 2 diabetes and cardiovascular diseases [Cooper et al, 2007]. Be that as it may, in human developmental history, insulin resistance could be a fundamental piece of typical homeostasis to encourage redirection of supplements to essential organs and a physiological versatile instrument for advancing our progenitor's survival in the midst of basic conditions, for example- starvation, contamination, injury and stress [Tsatsoulis et al, 2013; Johnson et al, 2012]. A similar instrument might be improperly actuated on an unending premise on the current obesogenic condition, prompting the appearance of hypertension, insulin resistance or metabolic disorder [Soeters et al, 2012].

Evolution by normal choice has been a focal arranging idea in biology. For many years, living creatures from organisms that are of lower level to people have been looked with survival stresses, including starvation along with diseases [Johnson et al, 2012]. The survival of multi-cellular creatures relies upon the life form's capacity for storing vitality for times when supplement accessibility is low or energy needs are high, and the capacity to battle contaminations [Blackburn, 2001]. To address the difficulties of contamination and other ecological pressure, an enacted resistant framework has a critical requirement for energy rich substrates that must be apportioned from interior and external energy

stores- (glycogen, proteins, triglycerides, or free unsaturated fats) [Straub, 2010]. An immune system that is activated ordinarily requires generous energy in a quiescent state. This prerequisite ascents into a functioning phase of inflammation [Straub, 2010]. Subsequently, the metabolic and immune systems are among the most essential prerequisites over the set of all animals [Sell et al, 2012 and Chandra, 1996]. It isn't astonishing then that metabolic and immune pathways that are developed to be firmly connected and associated and that the qualities controlling metabolic and pathogen-detecting frameworks are been exceedingly rationed from lower level life forms to well evolved creatures [Wellen et al, 2005]. As of late, new experiences have been increased through numerous cooperations amongst metabolic and immune system [Sell et al, 2012; Wellen et al, 2005]. An expanding group of proof proposes that energy metabolism is vital for the maintenance of inflammation that is chronic, as far as energy supply, as well as in the control of the resistant reaction through metabolic signs [Johnson et al, 2012 and Spies et al, 2012]. It is presently obvious that basic proteins are fundamental for controlling energy metabolism, for example, peroxisome proliferator-enacted receptors (PPAR γ), Toll-like receptors, and unsaturated fat restricting proteins. These basic proteins additionally go about as connections between supplements digestion and incendiary pathway initiation in insusceptible cells [Cipolletta et al, 2012 and Fernandez, 2012]. For instance, PPAR-γ, a master regulator of adipocyte differentiation, is likewise a noteworthy particle that usually drives the collection and phenotype of Treg cells' in fat tissue [Cipolletta et al, 2012]; and leptin, an imperative adipocyte-derived hormone to direct vitality homeostasis, can influence thymic homeostasis and the emission of intense stage reactants, for example- IL-1 and TNF α [Procaccini et al, 2011].

1.1. Finding out the link between diabetes and hypertension

According to the report of the American Diabetes Association, from 2000 to 2012, 71 percent of adults with diabetes had a blood pressure of greater or equal to 140/90 or were taking medications to help normalize blood pressure. There exists many people who have diabetes and also hypertension. Both conditions together can make them worse than ever [Barhum, 2017].

1.2. Hypertension and its treatment options

Another name of hypertension is high blood pressure. This leads to severe complications and increases the risk of, heart disease, stroke, and death. Blood pressure is generally known as the force exerted by the blood against the walls of the blood vessels. The pressure considered to be depended on the work that has being done by the heart and the resistance of the blood vessels. Medical guidelines identify hypertension- as a blood pressure higher than 130 over 80 millimeters of mercury (mmHg), according to guidelines issued by the American Heart Association (AHA) in November 2017.Around 85 million people in the United States are notified to have high blood pressure. Hypertension and heart disease are now considered to be global health concerns.

Types of Hypertension in Diabetes Mellitus includes, Essential hypertension, Hypertension consequent to nephropathy, Isolated systolic hypertension, Supine hypertension with orthostatic fall.

Treatment options of hypertension

Day to day required physical exercise:

Doctors recommend that patients with hypertension should engage in 30 minutes of moderate-intensity, dynamic, aerobic exercise. This might also include- walking, jogging, cycling, or swimming on 5 to 7 days of the week.

Reduction in the amount of stress:

By avoiding stress, or making development strategies for managing unavoidable stress, might help with blood pressure control. Using alcohol, drugs, smoking, and unhealthy eating to cope with stress will add to hypertensive problems. These needs be avoided [MacGill, 2017].

1.3. Diabetes

Diabetes is believed to be a gathering of metabolic illnesses in which there are high blood sugar levels over a drawn out period. This high blood sugar usually delivers the side effects of frequent urination, expanded thirst, and expanded hunger. Untreated diabetes can prove to be dangerous by causing numerous inconveniences. Acute complications incorporate- diabetic ketoacidosis and nonketotic hyperosmolar coma like

state. Genuine long term complications incorporate- heart disease, stroke, kidney failure, foot ulcers and harm to the eyes. All around, starting at 2013, an expected 382 million individuals have diabetes around the world, with type 2 diabetes making up around 90% of the cases. Worldwide in 2012 and 2013 diabetes brought about 1.5 to 5.1 million deaths for each year, making it the eighth driving reason for death. The quantity of people with diabetes, that is expected to rise to 592 million by 2035 [OMICS International, 2014].

Prevalence of diabetes:

The global epidemic of type 2 diabetes (T2D) can be taken as a major public health problem of 21st century and the fifth leading cause of death worldwide .The disease can also be considered as a leading cause of morbidity as contributing to development of, premature coronary heart disease (CHD), stroke, peripheral vascular disease, renal failure, and amputation. According to latest statistics released by the International Diabetes Federation, the number of people living with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030; 80% of these people with diabetes thought to live in developing countries. According to these predictions, in three leading countries with diabetes populations-USA, India, and China the approximate estimate of 23.7, 61.3 and 90 million people with diabetes in US, India, and China in 2011 will increase to 29.6, 101.2, 129.7 million by 2030 **(**Figure 1.3.1**) [**Sanghera and Blackett, 2012]**.**

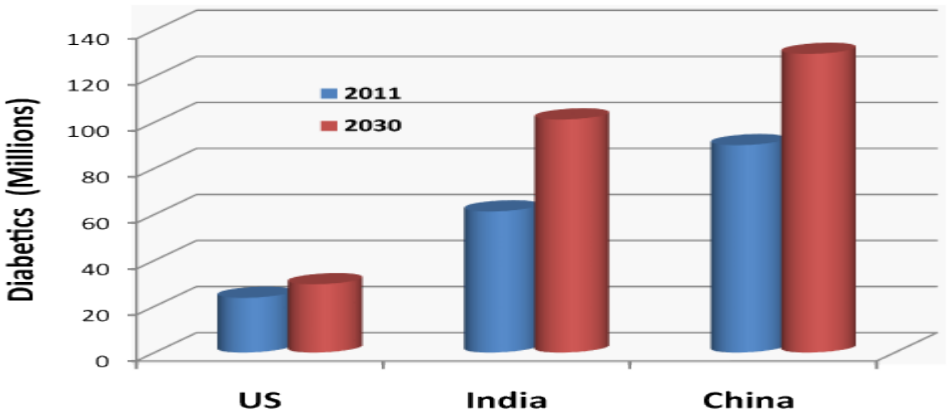

Figure 1.3.1: Prevalence of diabetes for the year 2011 to the projections for 2030 in US, China and India **[**Sanghera and Blackett, 2012].

Table 1.3.2: The state of diabetes in Bangladesh

Total adult population (1000s) (20-79 years)	95947
Prevalence of diabetes in adults (20-79 years) (%)	7.4
Total cases of adults (20-79 years) with diabetes (1000s)	7138.9
Cost per person with diabetes (USD)	41
Number of cases of diabetes in adults that are undiagnosed (1000s)	3,689.80

Table 1.3.3 : Types of diabetes and the percentage of affected people

No.	**Type**	**Definition**	**Percentage**	**Treatment**
1.	Type 1 Diabetes	The body does not create insulin	Around 10% of all diabetes cases are type 1	Good diet design, doing sufficient exercise, and taking insulin, can lead a typical life
2.	Type 2 Diabetes	The body does not create enough insulin for appropriate capacity	Roughly 90% of all instances of diabetes worldwide are of this type	Need to eat soundly, be physically dynamic, and test their blood glucose. They may likewise need to take oral medication, or potentially insulin to control blood glucose levels.

3.	Gestational Diabetes	This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose.		The majority of gestational diabetes patients can control their diabetes with exercise and diet. Between 10% to 20% of them will need to take some kind of blood-glucose-controlling medications.

The most basic diabetes side effects incorporating- frequent urination, extraordinary thirst and hunger, weight increase, unusual weight reduction, fatigue, cuts and wounds that don't heal, male sexual dysfunction, numbness and shivering in hands and feet. As the danger of cardiovascular disease has substantially thought to be higher for a diabetic, so pulse and cholesterol levels are needed to be checked regularly. Hypoglycemia - low blood glucose - badly affect the patient. Hyperglycemia - when blood glucose is too high - can likewise badly affect the patient [The MNT Editorial Team, 2017].

1.4. Insulin Therapy

In case of type 1 diabetes, insulin treatment- is known to replace the insulin that body can't deliver. Insulin treatment is required for type 2 diabetes and gestational diabetes at the time when different treatments started getting failed to keep blood glucose levels within the desired range. Insulin treatment is known to prevent diabetes complication in a way that helps in keeping the blood sugar within a target range [Mantzoros, 2016].

Figure 1.4.1: Negative consequences of insulin on the body [Walsh, 2016].

Insulin, that is necessary for life and along with the hormones, it should be balanced. In greater amount, this elevated insulin levels might have a host of negative consequences on the body of an individual.

1.5. Diabetes ,hypertension and problem solving computational tool

Hypertension is an exceptionally basic comorbid condition in diabetes. It influences around 20-60% of patients having diabetes which relies upon-obesity, ethnicity and age. Type 2 diabetes are at a high danger of inconveniences identified with hypertension [Cheng et al, 2017] .During the event of type 2 diabetes, hypertension frequently is being present as a feature of metabolic syndrome of insulin resistance that incorporates- central obesity and dyslipidemia too. Again, in the event of type 1 diabetes, hypertension might seem to be glimmer in the beginning of diabetic nephropathy [American Diabetes Association, 2003]. It is hypertension that builds the danger of both macrovascular and microvascular complications, including- stroke, coronary artery disease, and peripheral vascular disease, retinopathy, nephropathy, and perhaps neuropathy. Diabetes and hypertension regularly happen together. It is thought that there is a real cover amongst these diabetes and hypertension in etiology and ailment mechanism. The basic pathways incorporating-obesity, inflammation, oxidative stress and insulin resistance [Cheung and Li, 2012].Insulin, a hormone ushering glucose and different supplements into the cells. When there remains insufficient insulin or during the cells being impervious/resistant to the insulin's attempts giving glucose access, at that time the blood sugar levels climb and the hazard diabetes happens. In type 2, that is known to be insulin-resistant diabetes the body reacting in a way by directing much more of insulin, that brings about raised levels

of both glucose and insulin gradually. It exceeds 20 million Americans who have type 2 diabetes caused by insulin resistance. In any case, millions more—an expected 25 to 40 percent of the whole populace, have prior phases of insulin resistance. Considering these people, glucose levels are not hoisted, but rather their high insulin levels make different conditions turn out badly. Overabundance insulin generally gets related with expanded muscle to the fat ratio and obesity. It is seen irritating the ordinary metabolism of fats by raising cholesterol and triglyceride levels. It is also seen trapping intercellular communication, including- blood pressure regulating signals. It has the ability to energize/excite the sympathetic nervous system by making the heart pump with greater power and causing the arteries to get constricted. Also, it has been creating an unevenness in- sodium and potassium (which builds blood volume) and calcium and magnesium (which causes arterial constriction),by driving up blood pressure and gradually causing expand in the danger of heart disease [Lutsey, 2008 and Cohn, 2002].Moreover, Insulin can increase blood pressure by means of a few components: expanded renal sodium reabsorption, actuation of the sympathetic nervous system, change of transmembrane ion transport, and hypertrophy of resistance vessels. On the other hand, hypertension can cause insulin resistance in a way that modifies the delivery of insulin and glucose to skeletal muscle cells, which brings about weakened glucose take-up. The basic pathogenetic mechanism for both insulin resistance and hypertension might be an activation of the sympathetic nervous system. This outcomes in vasoconstriction, adding to the beginning of vascular structural changes and increment the quantity of fast twitch fibres [Salvetti et al, 2012]. Again, one of the essential fundamental reasons for hypertension, identified with body that creates excessively insulin and leptin because of a, high-carbohydrate and processed food diet. On rise in the levels of insulin and leptin, it causes blood pressure increment. Research published in 1998 in the journal Diabetes detailed that almost 66% of the test subjects who were insulin resistant additionally had hypertension, so the connection is critical. Hoisted levels of uric acid likewise altogether are connected with hypertension, so any program that is adjusted to address hypertension needs to help standardize both insulin sensitivity and uric acid level. As, with regards to prevent diabetes difficulties, normal blood pressure is given as importance as a greater control of blood sugar levels. There exists a few things that are useful to control both and these incorporates: controlling blood sugar, quit smoking, eat healthy, exercise most days, keeping weight in a sound range, stop drinking alcohol, limit utilization of salt, visit specialist consistently and so on [WebMD,

2017]. To overcome complications, the investigation of an unrivaled insulin dosing framework is essential. A dosing framework that considers different patient related factors(carbohydrate intake, physical activity, illness, body mass, insulin resistance and so on.) with a specific end goal to decide a more exact insulin dosage for individual patient may achieve better control of blood glucose and additionally make bring down cases other serious issues. Customized dose regimens might be figured utilizing a fuzzy-logic based system, where the framework gives an insulin dosing output, ideal to individual patients by considering several patient related factors. The fuzzy-logic based system, takes PRFs in account as information esteems and afterward produces a yield to give a more comprehensive insulin measurements for individual patients. This novel insulin dosing technique may help anticipate occurrences of different ailments as it relating to insulin therapy.

1.6. Why are diabetes and hypertension thought to be "co-morbidities"?

Diabetes and hypertension have a tendency to happen together in light of the fact that they share certain physiological qualities. Hypertension is a perilous ailment that turns out to be much more hazardous while there remains diabetes as well. Unfortunately, numerous individuals with diabetes, additionally influenced by ‘hypertension’, and the two infections normally happen together. Diabetes and hypertension happen together so as often as possible as a result they thought to be comorbidities (illnesses prone to be available in the same patient). On account of diabetes and hypertension, these impacts include:

i. Increased volume of the fluid

Diabetes, that increases the total amount of fluid in the body, and that tends to raise blood pressure. Insulin lowers the plasma glucose levels and is a key hormone in the improvement of diabetes mellitus. Insulin has a few capacities, including the accompanying: encourages glucose uptake by organs, advances glycogen storage in liver and muscle tissue, controls the breakdown of stored glycogen, advances fat tissue improvement, and controls fat resolution. Additionally, the insulin receptor being a part of the receptor tyrosine kinase family that incorporates platelet-derived growth factor receptor and heparin-binding epidermal growth factor-like receptor. By this way, insulin likewise stimulates the vascular smooth muscle cell movement and proliferation. Insulin that as a function to translocate Na+/K+-ATPase from the cytoplasm to the cell

membrane to open the Na+/H+ channel that inactively designated to transport hydrogen ions out of the cell and sodium ions into the cell. This procedure expanding the cell calcium ion concentration and decreases pH. The Na+/H+ exchange transporter gets opened followed by the decrease of intracellular sodium, and this caused by an insulin induced increase of Na+/K+-ATPase. The activity of Na+/K+-ATPase prompting sodium ions transport into vessels through renal tubule cells. When an insulin insufficiency leads to diabetic ketoacidosis the Na+/K+-ATPase activity gets decreased, which in turn increase the transport of sodium and hydrogen into the cell and potassium out of the cell. These changes taking place increase the cellular sodium ion density and lead to symptoms of high serum potassium. Again, when insulin resistance induces hyperinsulinemia the sodium reabsorption from renal tubules gets increased and this has leads to-hypertension. The circulatory fluid volume can likewise build in respect to hyperglycemia-induced hyperosmolarity. The prolonging high plasma glucose levels in diabetes cases alter the extracellular osmotic pressure on the side with higher concentration of glucose, this expanding in respect to the intra-cellular osmotic pressure. Water leaving the tissue (into the vasculature) for lessening the distinction between the intracellular and extracellular osmotic pressure and this flow expands the extracellular amount of body fluid and blood(i.e., circulatory blood volume). In this way, hyperglycemia in an addition leads to systemic blood pressure rise with increase in the circulatory fluid volume [Ohishi, 2018].

ii. An increase in arterial stiffness

Diabetes, decreases the blood vessels stretch ability by increasing average blood pressure. Diabetes, is thought can improve arterial stiffness through pathological changes in the vascular bed, for example- decreased nitric oxide bioavailability, increased oxidative stress, chronic low-grade inflammation, increased sympathetic tone and changes in type or structure of elastin as well as collagen in the arterial wall [Alvim et al, 2013].

iii. Impairment in insulin handling

Any changes in the way by which body produces and handles insulin, directly causes increases in blood pressure. The initiation of insulin therapy may be thought to be simple and uncomplicated in a few patients with type 2 diabetes, but in others, for the obese

patients, issues regularly emerge (ie, poor compliance, worsening B-cell function as well as insulin resistance) [Persson,2007].

The very much contemplated case of the self-reinforcing connection amongst diabetes and hypertension generally take place in the kidneys. The kidneys, that care considered to be the body's most important long-term blood pressure regulator. By the adjustments in the measure of salt and potassium in the body, the kidneys at last control how much fluid needs to be discharged as urine. This fluid regulating function helps to modulate long-term blood pressure, which physically controls how much liquid is available in the blood vessels [Persson, 2007].

1.7. Statistical and physical relationship between diabetes and hypertension

Statistical Relationship

People having diabetes, thought to be at a considerably more serious risk for the development of hypertension that amounts twice as regular in those with diabetes as in non diabetic people.

Physical Relationship

Diabetes causing hyperinsulinemia and raising the risk of hypertension. This condition that has thought to increases the measure of sodium that the body absorbs. It likewise advances the stimulation of the sympathetic nervous system. This causes change in blood vessel structure, which then affects the function of the heart and blood pressure [Anwer et al, 2011]. Figure 1.7.1 showing the interrelationship between the hyperglycemia and the hypertension through the intervention of insulin resistance, which are common link between the two diseases.

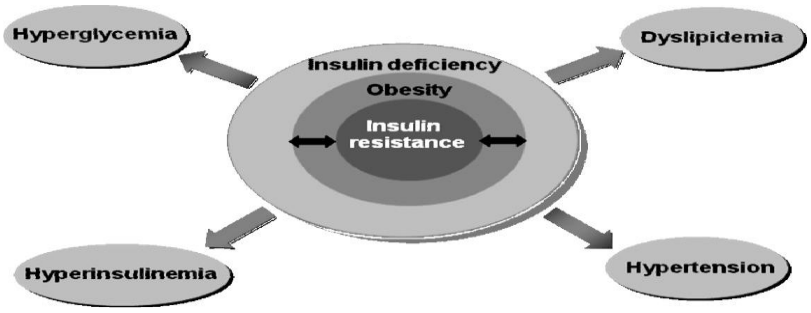

Figure 1.7.1: Metabolic syndrome [Anwer et al, 2011].

1.8. Common metabolic pathway between diabetes and hypertension

Diabetes and hypertension as often as possible happen together which has been mention earlier. There exists significant overlapping amongst diabetes and hypertension in etiology and disease mechanism. Obesity, inflammation, oxidative stress, and insulin resistance- are believed to be the regular or common pathways. Advances that is still ongoing in the comprehension of these pathways have been given new bits of knowledge and points of view. Physical activity, assumed to be a vital defensive part in the two ailments. The knowledge of the basic causes and illness components can permit a more compelling and proactive approach in their prevention and treatment measures.

1.9. The etiology of diabetes and hypertension

i. Genetics

Genome scans which includes, a huge number of subjects and controls have recently uncovered a substantial number of qualities with little impacts, rather than few qualities with extensive impacts anticipated originally [Zeggini et al, 2008 and Sober et al, 2009]. “Genetic variations” in the gene encoding angiotensinogen, adrenomedullin, apolipoprotein, and α-adducin- accounted for to be related with normal conditions, for example, diabetes, hypertension, dysglycemia, or metabolic syndrome [Ong et al, 2010 and Cheung et al, 2011]. Hypertension and diabetes significantly share basic pathways, for example- obesity, inflammation, oxidative stress, insulin resistance, and mental stress.

ii. Obesity

Obesity, that is a worldwide medical issue, recognized as the most vital hazard factor for hypertension and diabetes [Davy et al, 2003]. Obese people having an essentially higher danger of hypertension and type 2 diabetes [He et al, 2009]. Investigations of obesity in Western nations where there have high pervasiveness in prompted a more prominent comprehension of the wonder of hazard factor clustering and of the pathophysiologic links among hypertension, weight, diabetes. Obesity -generally considered as the joined consequence of dysfunction of feeding center in the brain, unevenness in energy intake and use, and hereditary varieties. Obesity is dictated by genes; around half to 90% of the variety in weight is the consequence of genetic predisposition as per twin studies [Loos

et al, 2003 and Maes et al, 1997] .Other diabetes-related genes incorporate-BCDIN3D/FAIM2, SH2B1, and KCTD15 [Cheung et al, 2010;Wang et al, 2010;Wing et al, 2010 and Ng et al, 2010] and in addition CRTC3, which has been appeared to slow down the speed of fat oxidation [Song et al, 2010]. It has proved nothing astonishing to find that diabetes and obesity share some common susceptibility genes.

iii. Inflammation and oxidative stress

Inflammatory markers eg, C-reactive protein (CRP) which expands in patients with diabetes, hypertension, and the metabolic syndrome, and furthermore anticipate the improvement of these illnesses [Blake et al, 2003;Blake et al, 2001 and Sesso et al, 2003]. The nearby renin-angiotensin-aldosterone framework (RAAS) assumes a vital part in vascular pathophysiology. Angiotensin-converting enzyme (ACE)- is expressed in the shoulder of coronary artery plaques. Angiotensin II (Ang II)- is to an extensive degree in charge of activating vascular inflammation and prompting oxidative stress [Savoia et al, 2007]. It stimulates NADH/NADPH oxidase, and enacts Rho/Rho kinase, protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) [Griendling et al, 1994; Yamakawa et al, 2000; Taubman et al, 1989 and Ushio et al, 1998]. Additionally, Ang II which down-regulates proinflammatory transcription factors, for example, nuclear factor-κB (NF-κB), that brings about the age and emission of receptive oxygen species (ROS), inflammatory cytokines (eg, interleukin-6 [IL-6]), chemokines, and adhesion molecules [Hernandez et al, 1997 and Schieffer et al, 2000]. These activities prompting the endothelial dysfunction and vascular injury. Gene regulatory network analysis that has recently uncovered oxidative stress as a key hidden molecular mechanism in diabetes and hypertension. The oxidative stress-mediated regulation cascade is the regular mechanistic connection among the pathogenesis of, diabetes, hypertension, and other related inflammatory ailments [Jesmin et al, 2010].

iv. Insulin resistance

Insulin resistance- related with impaired insulin signaling, debilitated fibrinolysis, and inflammation. With a raise in confirmation, recommending that insulin resistance might result from variations from the norm in key molecules of the insulin-signaling pathways, including- overexpression of phosphatases and downregulation as well as enactment of protein kinase cascades [Avramoglu et al, 2006], prompting anomalies in the expression and activity of different cytokines, growth factors, and peptides, and overproduction of

VLDL [Fonseca et al, 2004]. Insulin resistance- likewise result in impeded fibrinolysis, which portrayed by hypercoagulability and rise of fibrinogen and plasminogen activator inhibitor (PAI)- 1 [Meigs et al, 2000 and Grundy et al, 2004]. PAI-1 action gets hoisted in a wide assortment of insulin obstruction patients. Even in patients with typical glucose tolerance, raised levels of fasting insulin are related with disabled fibrinolysis [Meigs et al, 2000]. So it can be said that, insulin resistance is a prothrombotic state portrayed by a rise of PAI-1 and fibrinogen levels, prompting expanded danger of cardiovascular occasions [Fonseca et al, 2004 and Grundy et al, 2004]. Insulin resistance can be a consequence of an overproduction of proinflammatory cytokines (eg, IL-6, tumor necrosis factor (TNF), and CRP) and a relative inadequacy of anti-inflammatory cytokines (eg, adiponectin) that has been created from adipose tissues because of obesity [Eckel et al, 2005].

v. Mental stress and sympathetic nervous system

An additional connection exists between mental stress and obesity in patients with diabetes and hypertension. A high pervasiveness of hypertension in obese subjects has been identified with psychosocial factors, which includes- chronic stress [Bjorntorp,1991; Pickering,1999 and Narkiewicz,2002]. The hypothalamic– pituitary–adrenal axis was proposed as a key component connecting, obesity, hypertension, and chronic stress [Narkiewicz,2002 and Bjorntorp,2000]. So, individual are in need to decrease worry for escaping from the endless loop of mental stress, obesity, diabetes, and hypertension.

vi. Physical activity

Physical activity is known for lessening the danger of creating diabetes and hypertension. The mechanism then includes different changes in body weight, glucose tolerance, and in addition different factors [Cederholm et al, 1986]. The impact of obesity susceptibility genes on the beginning of obesity is affected by physical activity in the person. The genotypic impact of FTO is more articulated in- inactive than active people [Scott et al, 2010]. The advantages of physical activity in the anticipation and treatment of diabetes and hypertension are all around perceived yet general physical activity is troublesome and here and there difficult to do, in actuality.

Diabetes and hypertension share regular pathways, for example-SNS, RAAS, oxidative stress, adipokines, insulin resistance, and PPARs (Fig. 1.8.1). These pathways cooperate and impact each other and might even reason an endless loop. Hypertension and diabetes are both end results of the "metabolic syndrome". These may, consequently, create in a steady progression in a similar person. Central obesity- is the reason for the metabolic syndrome. Furthermore, advancement in way of life is a remained and is a foundation in the anticipation and treatment of diabetes and hypertension.

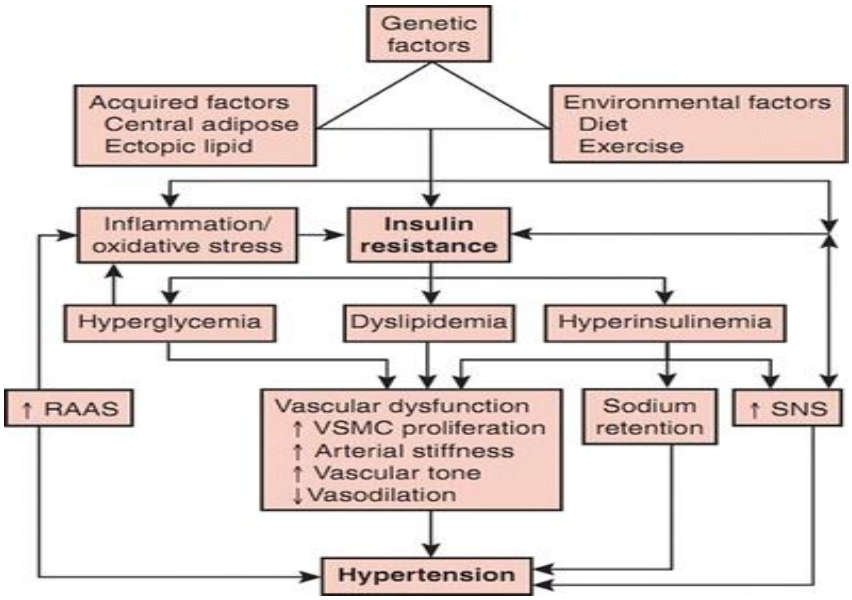

Figure 1.8.1: Summary of putative pathophysiologic mechanisms in the development of hypertension in diabetes mellitus [Mugo et al, 2017].

1.10. Ways to prevent both together

Lifestyle factors are the most ideal approach for bringing down the danger of hypertension and to keep up typical levels. There remains a wide assortment of confirmation, which has exhibited that by the control of blood pressure in individuals with diabetes can decreases the danger of complexities. An examination in the United Kingdom (U.K.) took after 1,148 individuals with diabetes for quite a long while. The members whose blood pressure was very much controlled had an altogether diminished danger of biting the dust from confusions identified with diabetes, hypertension, or both.

i. Weight loss

Loss of even a little measure of weight, might have any kind of effect in bringing down blood pressure. The National Heart Lung and Blood Institute (NHLBI) called for attention to that losing 10 pounds in weight can decrease blood pressure.

ii. Activity

Individuals who live with both “hypertension and diabetes” should attempt to be active no less than five days a week for no less than 30 minutes of the day. Regular activity known for bringing down blood pressure and offering numerous other medical advantages.

iii. Healthy diet choices

Individuals having diabetes should as of now be nearly in regular checkups of their eating regimen and keeping in mind the end goal to maintain blood sugar. They ought as far as possible the measure of salt in cooking and should abstain from adding salt to sustenance to help keep up blood pressure.

iv. Drinking alcohol in moderation

The lessening of alcohol consumption can help control hypertension. The intake of an excessive amount of alcohol generally prompting expanded blood pressure. Diminishing heavy drinking of alcohol diminishes the danger of hypertension.

v. Not smoking

Nicotine in cigarettes is known to increase blood pressure and heart rate. It also is known for adding stress to the heart and increases the risk of heart attack and stroke.

vi. Treatment with medication

Blood pressure medication- it is prescribed when blood pressure reliably staying over 140/90 for individuals with diabetes, regardless of way of life changes.

The main exemption might be for somebody whose blood pressure has been all around controlled for critical timeframe because of real way of life changes [Barhum, 2017].

Chapter 2: Purpose of the study

The purpose of the study is to find the relation between diabetes and hypertension so as to reduce the number of patients having both together that can be life threatening and introducing a way that can ensure better treatment measures by proving precise dose of insulin. We also observed whether the patients have knowledge about the treatments they have been gone throughout a long period of time and obtain required information that helped in our research purpose in determining the numerical difference between the physician's prescribed dose and the dose given as output by the MATLAB.

Chapter 3: Materials and Methods

3.1. Fuzzy Logic Approach

The idea of fuzzy logic was first advanced by Dr. Lotfi Zadeh of the University of California at Berkeley in the 1960s. Dr. Zadeh who was taking a shot at the issue of computer understanding of natural language. Natural language can not be effortlessly translated into the absolute terms of 0 and 1. It may see fuzzy logic as the manner where reasoning truly works and binary or Boolean logic, nothing but just a unique instance of it.

Fuzzy logic has appeared to be nearer to the manner in which our brains work. We aggregate data and shape a number of halfway/partial truths which we aggregate further into higher truths which thus, when certain thresholds are exceeded, cause certain further outcomes, for example, motor reaction. A comparative sort of process is utilized in neural networks, master frameworks and other artificial intelligence applications. “Fuzzy logic” is basic to the improvement of human-like capacities for AI, in some cases alluded to as “artificial general intelligence”: the portrayal of summed up human intellectual capacities in software so that, looked with an unfamiliar task, the AI framework could find a solution. [Rouse, 2016]

Fuzzy logic can be utilized to portray how information is processed inside human brains. For instance, it very well may be contended that people don't have a clue about the distinction amongst fat and thin. Five individuals might be fat and not have a similar seriousness of fatness. Or on the other hand, one individual may seem thin, contrasted with another, while both are really fat. Utilizing fuzzy logic, one can allot distinctive logic values for fatness, ranging from 0 to 1, as indicated by severity of fatness.

Fuzzy logic rationale is thought to be a computational paradigm that gives a mathematical tool for managing the uncertainty and the imprecision typical of human reasoning. A prime normal for fuzzy logic is its ability of communicating information semantically, enabling a framework to be depicted by straightforward, human-friendly guidelines. The fuzzy set framework has been used in a few unique ways to deal with demonstrating the diagnostic procedure.

Lately, computational knowledge has been utilized to solve numerous unpredictable issues by the creation of an intelligent systems. Fuzzy logic has turned out to be a great device for decision making systems. In conventional lead based approaches, knowledge is encoded as precursor resulting structure. At the point when new information are experienced, it is coordinated to the forerunners provision of each control, and those principles where precursors coordinate an information precisely are let go, setting up the resulting clauses. This process proceeds until the point when the coveted conclusion has come to, or no new manage might be fired. In the previous decade, fuzzy logic has turned out to be valuable for intelligent systems in medicine.

3.2. Notions of fuzzy logic

With a specific end goal to indicate how fuzzy sets theory and fuzzy logic are a suitable instrument in representation and dealing with medical concepts, three inquiries comes as a main priority: what is logic, what is fuzziness, and what significance has the term fuzzy logic [Hajek,1995]; and afterward, the utilization of fuzzy logic in medicine.
Logic- is thinking about the notions of consequences. The task of formal logic - to speak to this by means of well-defined logical calculi. Regularly, a logical calculus has two notions of consequence: syntactical (based on a notion of proof) and semantical (based on a notion of truth); at that point, there are the characteristic inquiries of soundness (does probability imply truth?) and completeness (does truth imply probability?).

Fuzzy logic in medicine:

The term fuzzy logic has two distinct implications—wide and narrow. In view of Zadeh's assessments on fuzzy logic, we may finish up two things. Initially, in the broad sense, everything dealing with fuzziness may be called fuzzy logic. Second, in the narrow sense, formal calculus of many-valued logic is the base of fuzzy logic. Now, fuzzy logic in medicine in a broad sense. In medicine, particularly in oriental medicine, most medical concepts are usually all fuzzy. The imprecise nature of medical concepts and their connections requires the utilization of fuzzy logic. It has defined inexact medical entities as fuzzy sets and providing a linguistic approach with an excellent approximation to texts. Fuzzy logic offer reasoning methods fit for drawing approximate inferences.

In rule-based fuzzy systems in medicine, experts often formulate their statement interms of rules of the type:
If x is A, and y is B, then z is C.

In this paper Diabetes related hypertension (systolic blood pressure) and ages are taken. The physician's medical knowledge is represented as a fuzzy relation between systolic blood pressure and age.

Reasons of using Fuzzy Logic

General observations about fuzzy logic that has been seen from recent studies shows,
Fuzzy logic is conceptually easy to understand. The mathematical concepts behind fuzzy reasoning are very simple. Fuzzy logic is a more intuitive approach without the far-reaching complexity. Fuzzy logic is flexible. With any given system, it is easy to layer on more functionality without starting again from scratch. Fuzzy logic is tolerant of imprecise data. Everything is imprecise if you look closely enough, but more than that, most things are imprecise even on careful inspection. Fuzzy reasoning builds this understanding into the process rather than tacking it onto the end. Fuzzy logic can model nonlinear functions of arbitrary complexity. You can create a fuzzy system to match any set of input-output data. This process is made particularly easy by adaptive techniques like Adaptive Neuro-Fuzzy Inference Systems (ANFIS), which are available in Fuzzy Logic Toolbox software. Fuzzy logic can be built on top of the experience of experts. In direct contrast to neural networks, which take training data and generate opaque, impenetrable models, fuzzy logic lets you rely on the experience of people who already understand your system. Fuzzy logic can be blended with conventional control techniques. Fuzzy systems don't necessarily replace conventional control methods. In many cases fuzzy systems augment them and simplify their implementation. Fuzzy logic is based on natural language. The basis for fuzzy logic is the basis for human communication. This observation underpins many of the other statements about fuzzy logic. Because fuzzy logic is built on the structures of qualitative description used in everyday language, fuzzy logic is easy to use.

3.3. MATLAB

MATLAB(matrix laboratory) is a fourth-generation high-level programming language and interactive environment for numerical computation, visualization and programming. MATLAB is being used in every aspect of “computational mathematics”. Following are some commonly used mathematical calculations where it is used most commonly: Dealing with Matrices and Arrays,2-D and 3-D Plotting and graphics, Linear Algebra, Algebraic Equations, Non special functions. MATLAB has been widely used as a computational tool in science and engineering encompassing the fields of physics, chemistry, math and all engineering streams. It is used in a range of applications including: signal processing and Communications, image and video Processing, control systems, test and measurement, computational finance, computational biology.

3.4. Experimental Materials and Methods

Patient population:

10 type 2 diabetes patients who are experiencing insulin treatment and suffering from hypertension as well were haphazardly chosen from the number of inhabitants in the city of Dhaka, Bangladesh; a patient pool which contains 6males and 4 females. The patients gave the accompanying data: systolic blood pressure, age and recommended insulin dose by the physician. In every one of the cases, the doctor ascertained an ostensible insulin dose in light of patient's age, blood pressure and afterward continued to alter the day by day measure of insulin given in agreement to resulting meeting sessions with the patients. Patients were notified about the strategies by which this information was to be utilized and assented to the use.

3.5. Calculation method for ascertaining insulin dosage

MATLAB was utilized for method development and examination of the gained information. The dose of insulin was figured by utilizing the fuzzy- based interface that had been in MATLAB. Each PRF (i.e. systolic blood pressure and age)was utilized as input factors in the framework and the resultant anticipated insulin dose was the yield. Two unique non-fuzzy based conventional techniques were utilized for computing insulin dose were incorporated to one framework to produce this yield. These standard

strategies were: estimation of insulin measurements in light of systolic blood pressure, calculation of insulin dosage in view of age. The fuzzy process incorporates 4 stages,

- Fuzzification
- Plotting the Decision Matrix
- IF/THEN rule setting
- Defuzzification

Table 3.5.1: Shows the two inputs used that are avg. systolic blood pressure , age and the insulin doses prescribed by their physicians

No. of patients	**Avg. systolic blood pressure**	**Age**	**Prescribed insulin dose**
1.	130	57	36
2.	120	62	20
3.	120	56	20
4.	110	48	18
5.	120	58	18
6.	160	56	20
7.	120	28	30
8.	150	56	20
9.	130	56	20
10.	140	65	30

Step 1: Fuzzification

Defining the fuzzy membership functions:

The MATLAB Fuzzy Logic Designer Toolbox had been utilized to decide the yield, in particular Insulin measurements (insulin dosage), against the sources of inputs, i.e. systolic blood pressure, age. Every one of the factors were fuzzified and the participation capacities were set to be triangular, with various extents. The systolic blood pressure and age had enrollment capacities with three fuzzy qualities Low (L), Optimum (O), High (H); The yield variable, insulin dose which had six fuzzy values- A, B, C, D, E and F.

Table 3.5.2 demonstrated the ranges of the INPUTS and the OUTPUT, considered for the framework.

Table 3.5.2: Ranges of the INPUTS and OUTPUTS

Input	**Input**	**Output**
Systolic blood pressure	Age	Insulin dose
100-190	15-75	18-58

Table 3.5.3: Breakdown of Fuzzy value and their ranges for Systolic blood pressure and Age

Fuzzy values	**Systolic blood pressure range**	**Age range**
L	100-130	15-35
O	130-160	35-55
H	160-190	55-75

Table 3.5.4: Ranges for Insulin dose

Fuzzy values	**Insulin dose**
A	18-26
B	26-34
C	34-42
D	42-50
E	50-58
F	46-54

For each input and output variable selected, we defined two membership functions (MF). We had to define a qualitative category for each one of them, for example: low, optimum or high. The shape of these functions could be diverse but we worked with triangles. For this reason we needed at least three points to define one MF of one variable.

As expressed beforehand, all the membership functions were been triangular. There were no area of overlapping membership in any of the variable. Figure 3.5.5 demonstrates the membership capacities (L, O, H) of systolic blood pressure.

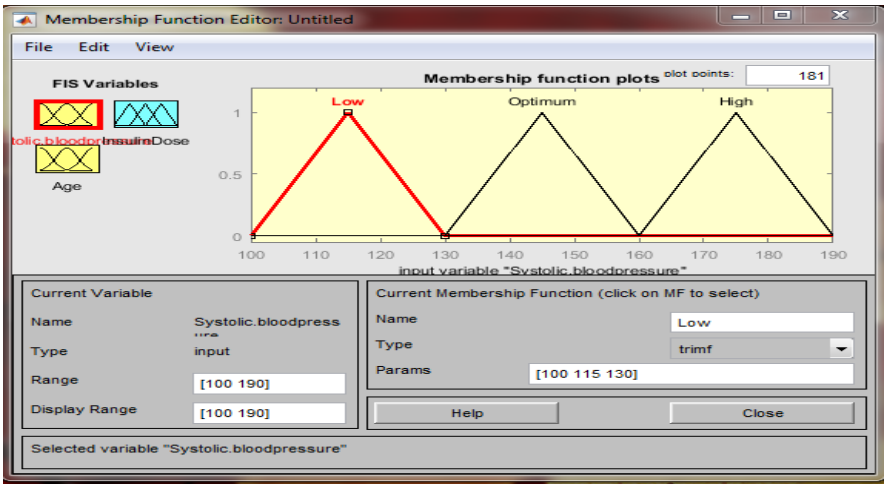

Figure 3.5.5: The membership functions of Systolic blood pressure

The three triangular membership functions (L, O, H) of age are illustrated in Figure 3.5.6.

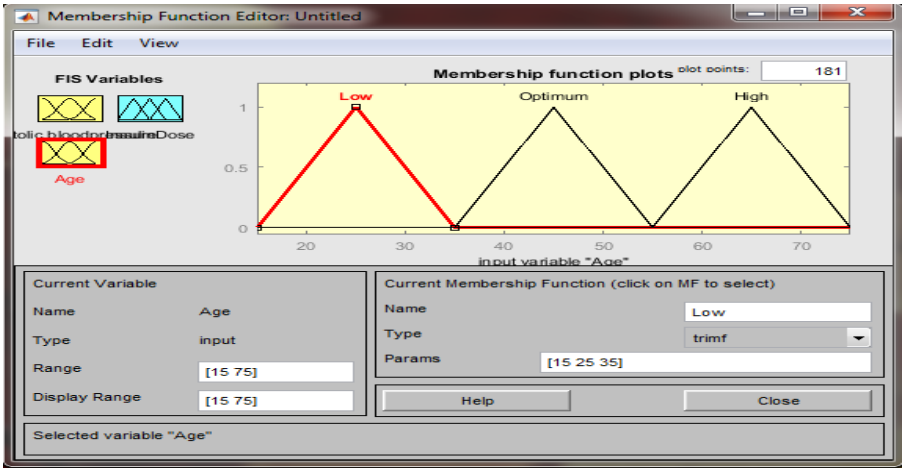

Figure 3.5.6: The membership functions of Age

The last set of membership functions of the system is that of the output, i.e. insulin dose- which includes six membership functions (A, B, C, D, E and F). Figure 3.5.7 illustrates the insulin dose memberships.

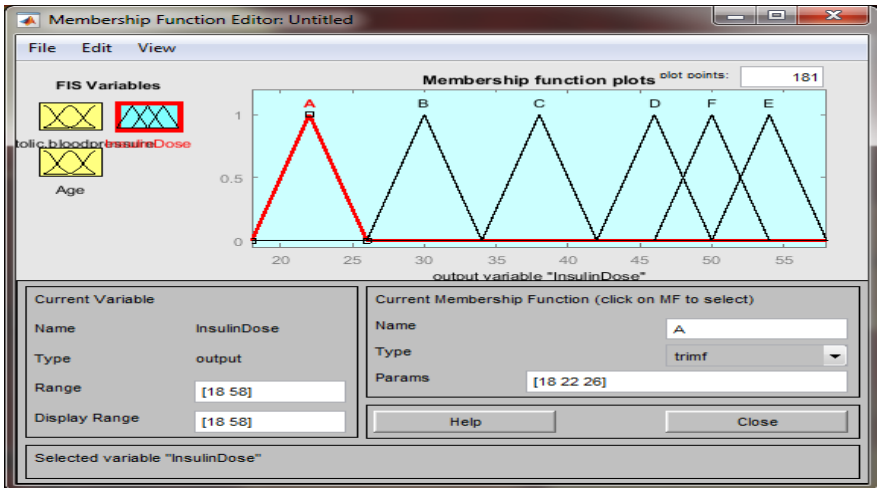

Figure 3.5.7: The membership functions of Insulin dose

To recapitulate, all of the above figures and tables illustrate that triangular functions were used in the fuzzification of all variables and in the membership functions of insulin dose .We could see an overlapping had taken place as an extra range F had been introduced for more perfection in administration of an accurate dose.

Step 2: Plotting decision matrix

Setting the rules for fuzzy inference:

Setting the standards for the input/output relationship prevailed after the meaning of membership functions, for fuzzy inference. That was the place the basic leadership had been sketched out. The if/then that point connections were utilized to set the rules for the inference. The system exhibited in this paper has 9 if/at that point rules. The principles are set by consolidating the participations of the two information factors (systolic blood pressureF1 and ageF2) to give an output (insulin dose). The decision matrices, had been utilized in setting the if/then that point rules, for insulin dose are appeared in the table 3.5.8.

Table 3.5.8: The decision matrix

Systolic blood pressure(F1)/Age(F2)	**L**	**O**	**H**
L	A	A	B
O	A	B	C
H	C	D	F

Step 3: If/then rule setting

The fuzzy if/then rules for the inference are set from the decision tables and are depicted as follows:

1.If(Systolic blood pressure is Low) and (Age is Low) then (Insulin dose is A)

2. If(Systolic blood pressure is Low) and (Age is Optimum) then (Insulin dose is A)

3. If(Systolic blood pressure is Low) and (Age is High) then (Insulin dose is B)

4. If(Systolic blood pressure is Optimum) and (Age is Low) then (Insulin dose is A)

5. If(Systolic blood pressure is Optimum) and (Age is Optimum) then (Insulin dose is B)

6. If(Systolic blood pressure is Optimum) and (Age is High) then (Insulin dose is C)

7. If(Systolic blood pressure is High) and (Age is Low) then (Insulin dose is C)

8. If(Systolic blood pressure is High) and (Age is Optimum) then (Insulin dose is D)

9. If(Systolic blood pressure is High) and (Age is High) then (Insulin dose is F)

Step 4: Defuzzification

Insulin dosage recommendation by defuzzification and surface diagrams :

After the sources of inputs/outputs were characterized and the rules were set, the last advance is the defuzzification of the system, where the system would restore a fresh incentive for the output, for this situation insulin dose. There are diverse techniques for defuzzification accessible in MATLAB. For this paper, the Centroid technique has been utilized, as this strategy has given close surmised outcomes for the subject under thought.

After defuzzification, a single crisp number suggestion, for insulin dose, was gotten. Figure 3.5.9 demonstrates a proposal for an insulin measurement of 38, returned by the fuzzy logic system after defuzzification, for a subject with a systolic blood pressure of 130 mmHg, an age of 57.

Figure 3.5.9: A recommendation of insulin dosage that is returned by the fuzzy logic system

The surface diagrams, provided in Figure 3.5.10 illustrate the relationships among systolic blood pressure, age and insulin dose.

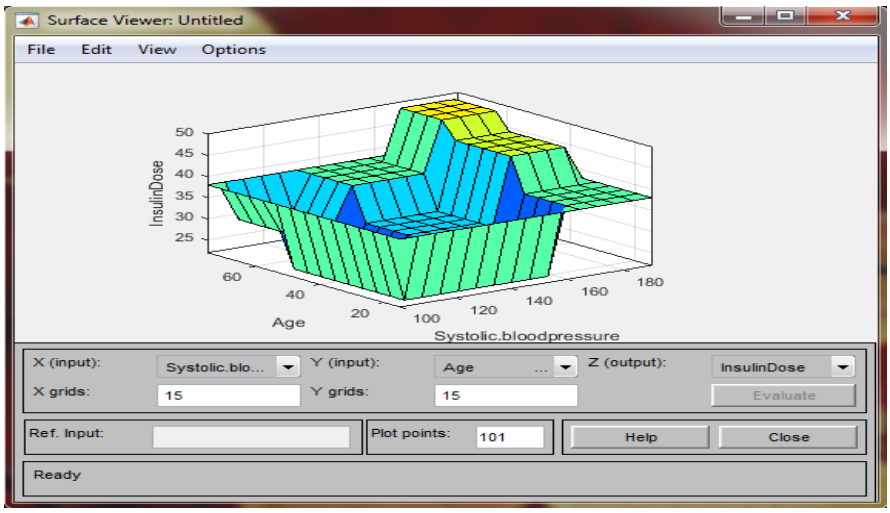

Figure 3.5.10: A surface diagram of insulin dose against systolic blood pressure and age

The surface diagram visualizes the relationships between variables, in this case systolic blood pressure, age and the output insulin dose.

3.6. The working method

At first we took the average systolic blood pressure(F1) of 10 patients. Then we took the age(F2) of that 10 patients. The 3rd thing is prescribed insulin dose which we didn't need to include in the decision table. The initiation of the work required "Excel" which included the datasets necessary for continuing our work. Considering the prescribed doses we divided it into 6 categories A,B,C,D, E and F at first. Here, we consider A=18-26,B=26-34,C=34-42,D=42-50,E=50-58 and F=46-54.Then we found from the data of avg. systolic blood pressure the (F1) values. Where the the L (low),O (optimum) and H (high) values are respectively (F1= 130, 120, 120, 110, 120, 160, 120, 150, 130, 120) so, the L (low) for F1= 110,H(high) for F1= 160 and thus the O (optimum) is (L+H/2= 110+160/2= 135)so the O is 135.Again, the ages of 10 patients were (F2=57,62,56,48,58,56,28,56,56,45) so here the L(low)=28,H(high)=62.So, the O(optimum) is (L=H/2=28+62/2=45) so the O is 45.We put the F1 values vertically and the F2 values horizontally in a table. We prepared an excel work which represents the methodologies that is the (value needed to set ranges) table where to find the F1 we select the Max value first column then (= max) in the ranges used in fuzzy page. Then we go back to the main worksheet page and select all the F1 values and thus we could find the max. value for F1.Again, we select the Min value and (=min) go back to the worksheet page select all the F1 and thus could find the min. value. Found the L and H for the F2 in the same manner. Then calculated the O for both of them. Then from all the calculated data we prepared separate tables for F1 and F2 with their specific ranges. Then, in the previous table where F1 lies in vertical line and F2 lies in the horizontal line, we placed the A,B,C,D,E and F(insulin dose ranges) according to those values. For the table which contains F1(systolic blood pressure) that was categorized by L,O and H and F2(age) that was too categorized by L,O and H the hypothesized insulin doses were placed. When, F1 is L and F2 is L the prescribed insulin dose can be A(18-26) as both systolic blood pressure and age are low the person required less units of insulin.F1 is L and F2 is O the prescribed insulin dose can be A(18-26) as age is in between optimum range and pressure is still low.F1 is L and F2 is H, here prescribed insulin dose can be B(26-34) as the factor age is high here but the pressure is still low. The gradual increase in age requires a bit increase in dose too as the ability to perform any kind of activity gradually decreases. F1 is O and F2 is L, here prescribed insulin dose can be A (18-26) as the person has low age and optimum pressure. Optimum pressure does not require

high dose of insulin.F1 is O and F2 is O, here the prescribed insulin dose can be B (26-34) as both factors are in optimum ranges. When both comes in an optimum range the previous dose may not work as desired so a bit increase in dose will work better in case of a diabetic patient.F1 is O and F2 is H, here the prescribed insulin dose can be C(34-42) as the factor age is high here so it requires more units of insulin. With the increase in age the dose also needs to be increased at a particular amount as with the increase in age the requirement for insulin also gets increased. It will require an increase more than the previous one where F1 is low.F1 is H and F2 is L, here the prescribed insulin dose can be C (34-42) as age is low but pressure is high. When a diabetic patient is diagnosed with high blood pressure and both started continuing together it can be because of insulin resistance so the dose is gradually enhanced according to the body demand with gradual increase in age but as, pressure is high here so, it won't require an enhance to extreme amount which can leave a patient with more adverse effects.F1 is H and F2 is O, here the prescribed insulin dose can be D (42-50) as the age is optimum and pressure is still high. During optimum age high pressure is not desirable.F1 is H and F2 is H, here the prescribed insulin dose can be E (50-58) as both factors are high. The dose needs to be increased to a maximum to get desired result and getting back the patient into his/her previous state. With the increasing trends in age if the patient is a type2 diabetic insulin resistance may occur so, enhanced units may require. But, this may give more rise in blood pressure so, the dose can also be a bit decreased and a new value in between D(42-50) and E(50-can be introduced that is F (46-54).The 2nd part of the work include "MATLAB" where we set systolic blood pressure and age as input so that we could get a precise insulin dose as output. For systolic blood pressure(F1) the ranges include L(100 115 130),O(130 145 160) and H(160 175 190).For age(F2) the ranges include L(15 25 35),O(35 45 55) and H(55 65 75).Similarly we divide the insulin dose within ranges A(18 22 26),B(26 30 34),C(34 38 42),D(42 46 50),E(50 54 58) and F(46 50 54). We divide them within ranges to observe the curves if any overlapping or discontinuity takes place. There were no overlapping in case of 1st and 2nd curves but the curve for insulin dose were a little different as we had introduced a new value of F there for more appropriate dose. We set 9 rules to observe the surface diagram. We also observe it after de-fuzzification by giving F1 and F2 as inputs because this gives us the precise amount of insulin doses that we could compare with the dose prescribed by the physician and could find the numerical difference.

Chapter 4: Results and Discussion

The patents in the example populace were picked indiscriminately who are living in Dhaka. These patients were at that point experiencing insulin treatment. The patients were given a questionnaire by which their knowledge about their health condition could be measured and to observe whether their physicians provided them the medications and dose of insulin considering both of the condition. Some of the patients had given us their opinion about the medication they were given like, a patient said that he was given the medicine Uromax, and this can cause him hypertension. Some of the patients gave us information regarding the medications they are taking that includes, Pantonix, Vestar, Betaloc, Amdocal, Amaryl, Lijenta, Tab.Metfo500mg, Galvus, Losucon, Bizoran .But most of the patients were not aware of the medications that they are taking .From the data that we have collected we could see that in most of the cases the administration of insulin increased the blood pressure as in case of a patient the average blood pressure before insulin was 160/80 and average blood pressure after insulin was 170/80,here we can see that it got increased. We have also found that most of them are provided with a diet chat and this may be a factor for their condition not reaching to a worst level. Then we insert the data as input in fuzzy system the prescribed insulin dose was also inserted as output, then we got new numbers by the MATLAB as output that is the predicted dose. Then the anticipated measurements for each of the 10 patients were then contrasted with the genuine recommended dosages by the physicians in Table 4.1.1. Table 4.1.1 additionally demonstrates the numerical contrasts between the two doses for every patient. The numerical difference between the anticipated and the recommended insulin measurements propose that there was an adjustment needed in light of the two patient related components (PRFs) gave. A few measurements were essentially extraordinary in contrast with the recommended dosages. We got both positive and negative numerical differences where positive may indicates hyperglycemic and negative may indicate hypoglycemic events. For instance on account of patient 6,8 and 9. Here the numerical difference in measurement was +18 units; as in the recommended dosage was essentially lower contrasted with the anticipated measurements. The measurement given by MATLAB, could be recommended to the patient as a superior fit, particularly considering the way that the patient experienced hypertension. Patient 6,8 and 9 were then watched for one entire week for observing whether the dose that had been prescribed by the physician could make any further changes that indicates recovery of

their condition or not. Along these lines, for this one case the higher measurements of insulin prompted better blood glucose direction. Just in the instances of 7 persistent was the numerical distinction a negative number. This implied the recommended measurement was higher than the dosage anticipated by the fuzzy system. Among the patient population, a typical pattern was seen as far as the recurrence of events of hypertension. This is the motivation behind why for various patients, the numerical differences were in the middle of +10. For these patients, a higher dosage of insulin may decrease the odds of these occasions and increment the personal satisfaction. Notwithstanding, it is critical to understand that if the insulin doses is too high, at that point insulin resistance may take place and likewise cause hurtful impacts which can lead to high blood pressure together with many other heart diseases as well and can cause death too. For instance, A 54-year-old female introduced subsequent to taking an overdose of an obscure measure of hydrochlorothiazide, doxazocin, atenolol and amlodipine. She was at first hard-headed to treatment with ordinary treatment (intravenous fluids, activated charcoal, glucagon 5 mg took after with glucagon drip, calcium gluconate 10%, and atropine). Besides, insulin at 4 U/kg was not successful in enhancing her hemodynamics. Soon after high measurement insulin was accomplished with 10 U/kg, there was dramatic improvement in hemodynamics bringing about three of five vasopressors being weaned off in 8 h. She was along these lines off all vasopressors following six extra hours. The part of high dose of insulin has been archived in earlier cases, anyway it is for the most part suggested after other regular treatments have failed. In any case, there are different reports that propose it as starting treatment. The patient failed conventional therapies and reacted well just with maximum dose of insulin. Doctors ought to consider high dose insulin early in severe beta blocker or calcium channel blocker overdose for development in hemodynamics [Seegobin, Maharaj, Deosaran and Reddy, 2018].

Table 4.1.1: Predicted dose vs. prescribed dose of daily insulin units for each of the 10 patients

Patient number	**Predicted insulin dose by the fuzzy system**	**Physician prescribed insulin dose**	**Numerical difference**
1.	38	36	2
2.	30	20	10
3.	30	20	10
4.	22	18	4
5.	30	18	12
6.	38	20	18
7.	22	30	-8
8.	38	20	18
9.	38	20	18
10.	38	30	8

Chapter 5: Conclusion

Since the fuzzy based system gives a more personalized figuring to every day insulin doses, it might make better direction for blood glucose levels for type 2 diabetes patients. This reality ought to eventuate once the patient blood glucose levels are checked over significant lots of time. For patient 6,8 and 9 specifically, the advantages could be obvious and the dose predicted by fuzzy could be to control both diabetes and hypertension and lessen the danger of occurring these together in further times that can lead to death. For this case, the fuzzy based framework could anticipate a more precise measurement prompting better blood glucose control. In one case, we could see that the predicted dose is less than the prescribed dose which has given a negative numerical difference, this can be because of his condition and other medical history researched by the physician but the dose predicted could be fit better with his condition if he had not developed insulin resistance. It is possible that these balanced measurements may mean better glucose control for different patients too however advance perceptions should be made all together for that claim to be decisive.

Control of hypertension and upkeep of perfect blood pressure is the questionable issue that would benefit the diabetic patient most. Pharmacists must end up being more wary about current tenets for the treatment of patients with cooperative hypertension and type 2 diabetes mellitus. Methodologies, for instance, understanding training and pharmaceutical appraisal can advance look after these patients and move back the movement to diabetic nephropathy. Various patients with diabetes mellitus and hypertension are not been managed according to rules. Specific hazard factors chose may help in recognizing patients at high-chance for lacking treatment. Patient and instruction supplier, general wellbeing methodologies, and health system changes are relied upon to address these issues. As the people turns out to be more settled and continues putting on weight, diabetes and hypertension will end up being altogether more ordinary. It is to be assumed that an approach like that plot here can confine their serious consequences.

5.1. Challenges

The main challenge during the study was to obtain the “as correct as possible” data from the patient population. Observing their previous and after, introduction of new insulin dose health outcomes(blood pressure and sugar level) as well as their continuing medication for about one week. Preparing the ranges in a way that there remain no chances for any kind of overlapping and any undesirable events. Working with small population in which most of them are not aware of the medications they are taking.

5.2. Future scope

We have worked taking 10 patients as our research subjects which shows that there exists difference in the dose prescribed by the physician and the dose that we get from MATLAB as an output. This tell us that their remains a bit of absence of the technological advances still in our medication providing system which can be a reason for a huge population suffering from both diabetes and hypertension together now-a-days. This can be life threatening as well. Fuzzy-logic is an approach which will help a huge population by providing a precise dose which can be a better one than the one given by a physician. If this small population could get benefit from such an approach so this is a matter of fact that the whole large population can also get benefit from this. If the dose will be prescribed in such manner than probably there will be less of such instances where these two gets life threatening. Technology has become a blessing for us now and if we can not make the use of that we will be lagging behind. The AI system has helped a lot in our research and it has more benefits as well in wider range.

AI technologies are being utilized or trialed for a scope of purposes in the field of human services and research, including detection of disease, administration of chronic conditions, conveyance of health services, and drug discovery. AI advancements can possibly help address imperative wellbeing challenges, however may be restricted by the nature of accessible wellbeing information, and by the powerlessness of AI to have some human qualities, for example, compassion.

AI can be utilized to analyze and recognize designs in substantial and complex datasets speedier and more definitely than has beforehand been conceivable [Leung, 2017].It can likewise be utilized to scan the logical writing for significant examinations, and to join various types of information; for instance, to aid drug discovery [Eves, 2015]. The

Institute of Cancer Research's canSAR database consolidates hereditary and clinical information from patients with data from logical research, and uses AI to influence expectations about new focuses for disease drugs. Researchers to have built up an AI 'robot researcher' called Eve which is intended to make the procedure of medication disclosure quicker and more economical[Williams,2015]. AI frameworks utilized in social insurance could likewise be significant for therapeutic research by coordinating reasonable patients to clinical investigations. Later on, it is likely that AI frameworks will turn out to be further developed and achieve the capacity to complete a more extensive scope of assignments without human control or input.

Chapter 6: Appendix

Diabetes Management Questionnaire

Dear Sir/Madam,

We are conducting a survey to understand the effects of blood pressure on daily insulin dosage as well as to understand the level of awareness of diabetes among the patient population. In this questionnaire, we are particularly collecting information regarding diabetes these topics.

Please answer the following questions as instructed. We assure you that the information you provide will be used for the purposes of this study only.

1. How much of insulin units are prescribed with daily?
2. Do you think obesity is responsible for both diabetes and hypertension?
3. Does the administration of insulin causes rise in your blood pressure?
   - Avg. blood pressure before insulin
   - Avg. blood pressure after insulin
4. Are you provided with a regular diet chart or exercise programs?
5. Are the medications given considering both disease conditions? If yes, name the medications provided. (If no, then just respond with "N/A")
6. Do you go for regular medical checkup?
7. Do you think that less stress at workplace can reduce the chances of hypertension?
8. Most of the times diabetes and hypertension occurs together.
9. Are you taking any other medication beside insulin that too can be the reason of hypertension? If yes, name the medications provided.(If no ,then just respond with "N/A"
10. Do you think that proper sleep can play a vital role to keep the blood pressure within normal range?

Chapter 7: References

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