

Role of Diabetes and Blood Pressure in the Advancement of Renal Disease

Chaudhary MJ Nazar^{1*}, Bojerenu M Mauton² and Manzoor A Lala³

¹Department of Medicine, Ealing Hospital, UK

²Department of Internal Medicine, Howard University Hospital, Howard University, Washington, USA

³Department of Public Health, Public Health Development Services Ltd, UK

Abstract

Bulk of the kidney disease in diabetic patient are associated with nephropathy complications. Hypertension is usually found in chronic type 1 and type 2 diabetes sufferers. Numerous factors like vascular remodelling, basement membrane thickening, vascular atherosclerosis, mesangial cell proliferation, oxidative stress in renal apparatus due to ischemia etc. due to both the hypertension and hyperglycemia leads to expansion and evolution of nephropathy in these patients. Management of hypertension is therefore highly advisable in diabetes patient as an important intervention to prevent vascular damages like nephropathy. The aim of hypertensive drug management in diabetic patient should include both the management of blood pressure as well as albuminuria management. ACE inhibitors are found to be the most appropriate drugs which complies to both these requirement while the use of other antihypertensive drugs require caution due to their derogatory influences on the glucose and lipid metabolism in diabetic patients.

Keywords: Kidney; Diabetes; Hyperglycemia; ACE inhibitors; Albuminuria; Antihypertensives

Introduction

Diabetes mellitus and hypertension are two of the most common diseases in Westernized, industrialized civilizations, and the frequency of both diseases increases with increasing age. Diabetic patients are always on a high risk of developing diabetes related complications like hypertension, neuropathy, nephropathy, retinopathy, stroke and others. Hypertension usually develops after chronic uncontrolled or under-controlled diabetes and then participates in the progress of diabetes nephropathy [1].

This nephropathy normally develops after 15 years of dual exposure of diabetes and hypertension. Observations over-the-years suggest that one-third of the diabetic patient develops diabetic nephropathy which on long turn leads to chronic renal problems. It is well appreciated both that coexisting hypertension exacerbates diabetic nephropathy and that diabetic nephropathy somehow results in a markedly increased risk of hypertension [1].

These individuals constitute for 90% of the patients with dual diagnosis of hypertension and diabetes. It is therefore essential to isolate the menace issues associated with the advancement of diabetic nephropathy. It is also highly advisable to have better knowledge of early treatment procedures so that extensive morbidity and mortality can be avoided [2].

Aim and Objectives of the Study

Since the population of hypertensive diabetic patients are increasing due to changes in lifestyles as well as ageing population around the world, it is important to completely understand the interrelationship between the two illnesses. Also blood sugar nephropathy is a major factor of development of final phase renal diseases which accounts for high number of mortality and extensive morbidity and therefore understanding each and every step of its development and progression is crucial. It has been found that prevalence of diabetic nephropathy is greater in the hypertensive blood sugar patients in comparison to the other diabetes patients without hypertension. The goal of the literature review is therefore, "to identify the underlying mechanism by which diabetic nephropathy is interrelated with chronic hypertension and diabetes."

Main objectives of the study are as below:

1. To identify the research based on diabetic nephropathy in

hypertensive patients.

2. With reference to the available pathophysiological knowledge, identify the mechanism by which all the three conditions i.e. hypertension, diabetic nephropathy, and diabetes are interrelated.

3. To understand how the anti-hypertensive treatments restricts or prevent the progression of diabetic nephropathy.

Methodology

Porter says that an approach is devoted to the methods employed for collecting pertinent suggestions to react to the investigation query [3]. A literature review could only be useful and instructive if a suitable procedure is adapted to recognize and frame a responsible study [4,5]. These types of methodical exertion lead to superior appreciation of the subject and therefore propose a publically beneficial work. This section explains the various steps performed for an effective methodology.

Identifying search terms and synonyms:

Search terminologies even recognized as important terminologies and synonyms utilized for this methodical assessment are shown in the underneath table (Table 1):

Search strategy:

Aveyard has procured four diverse approaches for locating the pertinent facts and statistics in accord with the investigation query [6]. The four approaches are expounded underneath:

1. Locating electronic databank: Important words and the stated search terminologies are explored in the electronic databank. For this methodical appraisal, electronic databank examined were Ovid SP, Medline, Ovid SP, Pubmed, Embase, Web of science, Cochrane library, and Google scholar.

To increase the authenticity and accuracy of the search, Boolean

*Corresponding author: Chaudhary MJ Nazar, Department of Medicine, Ealing Hospital, UK, Tel: +44 20 8967 5000; E-mail: dr.cmjnazar@live.co.uk

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Important terminology	Synonyms
Diabetes	<input type="checkbox"/> Diabetes mellitus
	<input type="checkbox"/> Diabetes type 1
Nephropathy	<input type="checkbox"/> Diabetic nephropathy
	<input type="checkbox"/> Nephropathy associated with diabetes
	<input type="checkbox"/> Renal disorder related to diabetes
Hypertension	<input type="checkbox"/> High blood pressure
	<input type="checkbox"/> Chronic hypertension

Table 1: Important Terminologies and synonyms.

operators were utilized. Boolean operators are used for conjoining two terms or expressions in unison. The operators utilized in this pursuit approach were AND, OR and NOT. The usage of 'AND' is undertaken to limit the pursuit by assimilating the search terminologies in unison and thereby making the quest more concentrate. On the other hand, the Boolean 'OR' is utilized to add a synonym with the stated search terminologies. This is undertaken to increase and broaden the transcript pursuit. The Boolean 'NOT' is utilized unambiguously to evade and eradicate needless expressions or conclusion that could be tremendously inconsistent to the result endings.

Cornack (2000) mentions that regular truncation such as " ? \$ + * , were utilized at the closing or opening of the key-phrase to recognize the deviations comprising the root. This approach aids in locating both singular and pleural manners of the recognized search terminologies.

2. Snowballing: This approach evaluates the references of the stated investigations to enhance the statistics pool.

3. Hand searching: The researchers manually looked into published sources such as articles, periodicals, administrative reports, and bulletins. Anglia Ruskin Library furnished with the entire published papers.

4. Interviewing the author: The final approach of fact location had the investigators interviewing the writers or the representatives of institutes to attain the omitted info or to augment the info. This approach was unfortunately left out in this research plan.

Criteria for Selection of the Studies

Deliberation of including and excluding conditions aids the scholar to isolate accurate and definite literature review applicable to the current investigation query. The inclusion conditions are even recognized as suitability conditions and thereby firmly postulate the features of investigative populace and categories of interferences to be utilized. Inspecting it closely, the exclusion conditions stipulate the undesirable features of the tester populace [7]. To achieve operational, concentrated, and filtered quest, one strongly recommend that the investigation conforming to the inclusion and exclusion conditions must just be utilized in a methodical assessment.

Inclusion criteria

1. Any studies published over the years related to the topic.
2. Studies evaluating the diabetic nephropathy in hypertensive patients.
3. Studies available as full articles.
4. Works available in English.

Elimination conditions

1. Works available in only abstract form were excluded.
2. Studies observing the effect of hypertension on other diabetic complications like neuropathy, kidney failure, etc.

Quality Assessment of Selected Studies

Quality appraisal

Methodical assessments are attaining prominence in numerous domains such as medical science, learning centres, and infirmity and recuperation. The leading cause of this popularity is the intrinsic form of methodical appraisals to minimalize prejudice with regards to position, assortment, coding, and gathering of the investigations. The thoroughness by which prejudice is diminished calls for a systematic development of these assessments.

Quality assessment of the chosen investigations is crucial to measure value of approach and investigation design added with abolition of inferior value investigations. The researches chosen for this methodical appraisal were evaluated for value assessment by the instrument provided by Cochrane database for appraisal of the studies.

Validity, reliability, and trustworthiness

Validity and dependability are significant devices for acute valuation of any research. Joppe (Figure 1), says that "The extent to which results are consistent over time and an accurate representation of the total population under study is referred to as reliability and if the results of a study can be reproduced under a similar methodology, then the research instrument is considered to be reliable." The assortment of investigations in firm accord to the prearranged insertion and exclusion conditions ensures reliability in the investigation. Strict assortment of researches for the methodical examination makes it both dependable and reproducible [8].

Joppe defines validity as, "Validity ascertains if the investigation really evaluates that which it had envisioned to evaluate or the accuracy level of the investigative outcomes. Alternately, we could ask the question if the investigation device permits people to hit "the bull's eye" of the investigative purpose. Scholars usually ascertain legitimacy by looking for a number of queries, and would frequently seek the solutions in previously undertaken investigations." The objective of the current research was to ascertain the efficiency of treadmill exercise in the treatment of heart attack. The investigations chosen for the methodical examination supplied precise and straightforward info about the investigation query. Furthermore, usage of quality appraisal tools established the assortment of just the highly suitable researches. The current investigation aided to comprehend both the efficiency of several types of treadmill exercise and the involved machinery [8].

Dependability of a investigation establishes that the proofs employed to submit any specific outcome are thorough and the resultant outcome delivers strong basis [5]. As the current research was basically a quantitative methodical study, dependability of the research is revealed by its rationality and dependability features.

Ethical considerations

An investigation comprising testing on human or animals should consider specific moral concern. These practices are essential in maintaining the respect and privacy of the investigative matter. Moral concerns are encoded by explicit ethics board and it is essential for the investigator to rigidly pursue them in the course of the investigation [9].

As the current investigation was a methodical appraisal hence there was no involvement of any mortal or animal therefore there was no need to get permission from any ethics board. Nevertheless, valuing the maxim of ethical concern, only those studies were selected which stringently followed the ethical consideration and had ethics committee clearance.

Data extraction

Data extraction reveals the purifying of pertinent researches from entire attained facts. In general 169 abstracts were acquired originally from the chosen databanks. After eliminating imitations 98 abstracts were left. Out of these abstracts 63 were omitted for their deviations with investigative query, remaining 35 theorizes and researches were completely studied from which 14 matched wholly with inclusion conditions. Although 6 studies were excluded as they were not showing significant score on the quality appraisal scale. The remaining 8 articles were later deliberated for methodical appraisal. The entire method is symbolized in an illustrative manner in the chart shown underneath (Figure 2).

Literature Review

Underlying mechanism of hypertension and nephropathy development in a diabetic patient

Increased Platelet adhesion and platelet aggregation: Both the platelet bonding and combination processes are observed to enhance in both blood sugar mellitus as well as hypertension. Although the exact mechanism for such changes is very complex and not completely understood yet, it is supposed that these changes occur due to altered intracellular divalent cation metabolism. Both the Ca^{2+} and Mg^{2+} ions play crucial role in managing platelet aggregation and adhesion as the calcium ion increases the process while the magnesium inhibits it. It has been observed that calcium ion concentration in the body increases with increase in lipoprotein (usually observed in the diabetic patients) even if the patient has hypertension or not. Also the parallel judiciary hyper aggregation also aggravates in the non-insulin reliant blood sugar mellitus with or without the complaint of high blood pressure. Findings suggest that all the diabetic patients show increased calcium ion concentration and reduced magnesium ion milieu which directly contributes to such unbalanced processes inside the body. Uncontrolled and unnecessary platelet aggregation and adhesion leads to the narrowing of microvasculature which in turn may be one the reason for ischemic shock and the following inflammatory cascade and oxidative stress [9].

Abnormalities of platelet function in diabetes mellitus and hypertension

Coagulative and fibrinolytic activities inside a hypertensive diabetic patient get unbalanced. It is reported that the procoagulation state in such patients is highly activated due to increased circulating levels of different coagulation issues. For instance, the endothelial derived von Willebrand issue increases in response to vascular injuries, inappropriate glycaemic control, and injury to endothelium. High levels of factor VIII which presents because of uncontrolled blood glucose levels and

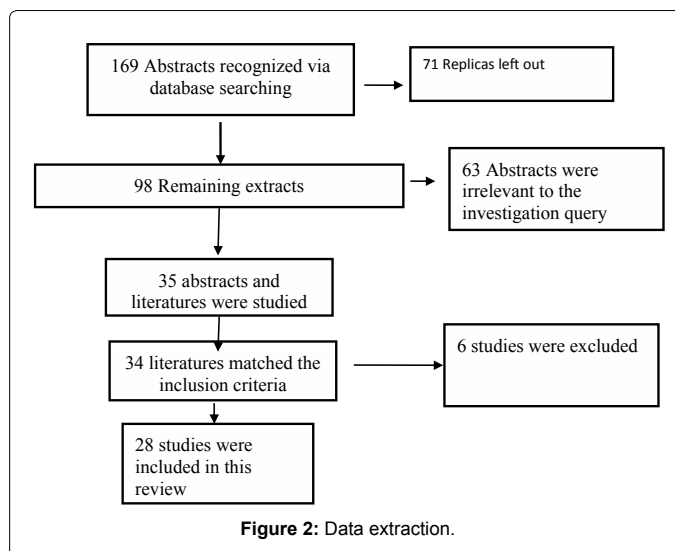


Figure 2: Data extraction.

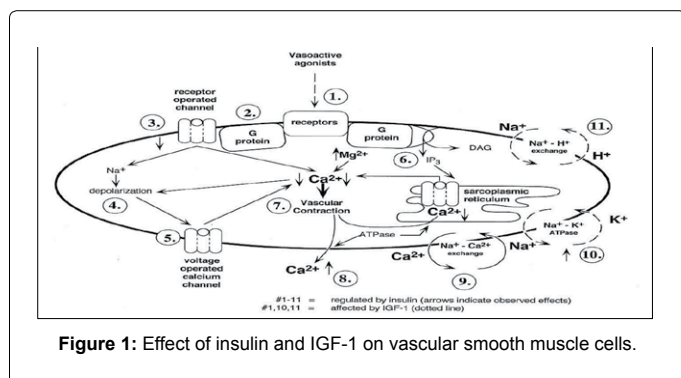
high lipid levels for a prolonged period of time enhances the thrombin formation processes leading to occlusion of the microvasculature. Other coagulation factors like factor VII and fibrinogen also increases in hypertensive diabetic patients leading to clot formation. Elevated stages of PAI-1 are perceived in the blood sugar sufferers having uncontrolled hypertension or the patient with myocardial infarction thus leading to enhanced coagulation inside microvasculature. These findings suggest that high lipid levels, uncontrolled hypertension, and reduced glycaemic control are independent menace issues for the growth of microvascular problems like diabetic nephropathy [10,11].

Lipoprotein abnormalities

Insulin resistance or high insulin levels in the circulations contribute to the growth of atherogenesis in diabetic hypertensive sufferers, especially in type 2 blood sugar mellitus sufferers. One of the main reason for this is high levels of circulating lipoproteins. Lipoproteins have a structural homology with apolipoprotein(a) and thus bind with fibrin to inhibit the fibrinolysis. Hindered fibrinolysis causes delay in thrombolysis and thus accelerates plaque formation in the microvasculature [12].

Oxidised LDL are not recognised by their respective receptors but are taken up by the macrophage scavenger receptors. Such uptake of oxidised LDL by the foam cells protects the LDL molecule from degradation. Accumulated oxidised LDL thus leads to alternations in the morphology as well as functioning of the endothelial cells and produce irreversible damage. Furthermore, oxidised LDL attracts monocytes to the damaged endothelium which gets attached to them and then carries the damaged cells in the circulation of internal vasculature [13].

The non-enzymatic linkage of glucose molecule to the proteins which is known as glycosylation process increases in the diabetic and hypertensive patients with high LDL levels. Glycosylation negatively affects the action of apolipoprotein-a which is responsible for receptor mediated uptake of circulating LDL and therefore its degradation. Absence of apolipoprotein-a action renders the LDL circulating in the blood stream which in turn accelerates the atherosclerosis process [14]. Glycosylation of LDL also occurs and the glycated LDL are highly immunogenic which triggers the antigen-antibody inflammatory pathway. Binding of the LDL to the antibody leads to the formation of foam cells and accelerated platelet aggregation leading to microvascular damage. Also the glycated LDL get bound to the local matrix proteins by virtue of its characteristic of forming glucose mediated cross links.



Following this bonding, oxidative stress starts and damages the matrix [15].

Role of endothelial dysfunction

The lipoprotein lipase activity of the endothelium is lost in the state of insulin resistance. These leads to the increased amounts of cholesterol ester enriched extremely low concentration lipoproteins which are not getting converted to low-density lipoproteins. High levels of these circulating VLDL are injurious to the endothelium once they are taken inside via the receptors.

It appears that hyperglycemia also contributes in the progression of endothelial dysfunction as it activates the protein kinase C enzyme. The high levels of these enzyme triggers the production of different inflammatory factors like prostaglandins. All the factors (Angiotensin-converting enzymes, platelet aggregation factors, endothelia, and vascular growth factors.) together increases the vascular reactivity and thus leads to unnatural growth and remodelling of the vasculature initiating the ischemic pathways. Endothelial cell matrix is also affected in the similar way by these factors and therefore basement membrane thickening is observed in the patients with uncontrolled hyperglycemia. Collagen synthesis and thus its deposition is also increased in the state of hyperglycemia as the condition aids in the increased synthesis of endothelial cell collagen IV and fibronectin [16,17].

Changes in vascular endothelium in hypertensive diabetic patients

Underlying metabolic and hemodynamic changes occurring a hypertensive diabetic patients also leads to alternations in the vascular endothelium. Both high cholesterol levels and high blood glucose levels together impairs the endothelium-dependent relaxation of vasculature system [17].

Insulin as well as IGF appears to have important negative effects on the endothelial cells. It is already reported that insulin affects the glucose-mediated triggering of the protein kinase C and diacylglycerol in these cells. A hypothesis suggest that uncontrolled blood glucose levels relates to such enhanced protein kinase C activity in vasculature of a diabetic patient which further leads to the complications like extensive vascular tone, initiation of atherosclerosis, and increased permeability and ultimately microvascular damage. The hypothesis is again confirmed by the finding that control of blood glucose levels following an insulin treatment prevents activation of these enzymes [17]. Both these findings combine to prove that impaired insulin action as seen in the non-insulin reliant blood sugar sufferers having hypertension is the main reason for endothelial dysfunction. However, another report also provide information that although hypertension do not alter the carbohydrate metabolism or induce the lipid changes; its various characteristics maintains the increased vascular tone and thus excessive endothelial vasodilation brought up by diabetes [18]. This finding provide additional credibility to the hypothesis suggesting microvascular damage in the hypertensive diabetic patients.

Vascular smooth muscle cell (VSMC) abnormalities related to insulin and insulin-like growth factor (IGF-1): Both the insulin and IGF-1 have important metabolic effects on the vascular smooth muscle tissues as both the hormones regulated these cells cation metabolism. Effect on the cation metabolism not only helps in glucose uptake and metabolism by the cells but also aids in managing their contraction and relaxation. Insulin and IGF-1 exert their effects in a paracrine and autocrine fashion. While insulin requires to pass through the endothelium to exhibit its effects on VSMC, IGF-1 is synthesised by the cells themselves. Both insulin and IGF-1 have same receptors and

pose similar actions. The hormones increases the Na^+, K^+ -ATPase activity and therefore reduces the calcium ion concentration inside the cells. Insulin also opens the sodium channels and thus leads to reduce intracellular calcium concentration. The contractive property of the vasculature is thus attenuated by the paracrine and autocrine effects of the hormone and the vasculature is dilated which leads to improved blood flow to the regional vasculature bed. This process also helps in the regulation of blood pressure. However, in the diabetic individuals with resistant insulin receptors, the dilatory effect of both insulin and IGF-1 is lost which leads to reduced blood flow to vascular bed and thus triggers the ischemic inflammatory pathway which is responsible for oxidative stress and thus damage. Uncontrolled blood pressures in insulin resistant diabetic patients can also be explained by the same theory [19].

Persistent hyperglycemia and vascular abnormalities in the hypertensive diabetic patient

Persistent uncontrolled high blood glucose levels have been found associated with the exacerbation of vascular complication due to both the blood sugar and hypertension. Poisonous influence on vascular endothelial membranes mediated by high circulating blood glucose levels is independent of the osmolality [20].

The toxic effects caused by the chronic hyperglycemia in an hypertensive patient includes reduced endothelium nitric oxide mediated vascular relaxation and therefore extended vascular constriction; hyperplasia of the vascular smooth muscle membranes, alternations in the vascular architecture; and progression of the atherosclerosis. All these events not only lead to inflammatory damage and oxidative stress but also to the development of chronic hypertension in the patient [21].

A literary report by Roy et al. on the cultures of human vascular cells [22] found that high glucose levels were able to trigger overexpression of fibronectin and collagen IV. Therefore it can be established that the persistent high blood glucose levels as perceived in undermanaged blood sugar sufferers which is leading to the extensive actions of fibronectin and collagen IV is also one of the factor responsible for dysfunction of endothelial cells. Fibronectin by virtue of its cell matrix interaction property therefore leads to vascular damage along with coagulating of the basement tissue in the glomerular apparatus and hyperplasia of the mesangial layers [22].

As discussed earlier, persistent high blood glucose levels even causes the creation of non-enzymatic glycosylation end products which have a crucial part in the development of atherosclerosis and vascular restructuring. Glycosylation of the collagen makes it more resistant to the digestion by the protein collagenase. The glycosylated collagen then binds to the other non-glycosylated proteins like LDL. Crosslinking of the two increases the susceptibility of internal intima for oxidation. This is the main mechanism by which vascular damage and diabetes leads to the complications like angina and congestive cardiac failure. The vascular damage to the renal apparatus especially glomerulus affects the glomerular filtration rates which in turn activates the renin-angiotensin system. Instigation of this structure exaggerate the hypertensive state of the diabetic patient [22].

Vascular effect of non-enzymatic protein glycosylation and hypertension

Advanced glycation end products are present in abundance in a persistent hyperglycemic patient. It has been recognised that these end product proteins can bind to specific membrane-associated macrophage receptors. These binding in turn leads to the production and release

of cytokines like tumor necrosis factors and interleukin-1. Cytokines trigger the protein synthesis pathways in the cell and compel them to proliferate. Furthermore, these advanced-glycation end products (AEG) also enhance the secretion of the platelet-derived growth factors which allows increases endothelial cell permeability. AEG also acts as chemo-attractant for blood monocytes. All these factors together contribute to the proliferation of extracellular matrix and proliferation of the vascular smooth muscle cells resulting to vascular hypertrophy and remodelling. Reduced elasticity of the micro and macro vasculature has many consequences and diabetic nephropathy is one of them. The damage is more severe in the patient with hypertension as the condition leads to sustained vasoconstriction due to reduced activity of endothelial derived vasodilator like NO. Narrowing of vasculature as well as constant vasoconstriction not only leads to vascular changes in endothelium but also predispose the patient to chronic hypertension [23].

Other reason for endothelial changes and hypertension in diabetic patient is increased sodium reabsorption. A glucose and sodium cotransporter system exists in the renal tubules. High glucose levels in the urine of a diabetic patient activate this transport mechanism and high amounts of sodium are transported back to the blood stream. While high sodium levels increases the blood volume and therefore increases blood pressure via renin-angiotensin aldosterone system; the persistent high glucose levels lead to vascular remodelling and constriction. It is also reported that high insulin levels in the case of insulin resistant diabetic patients can also increase sodium reabsorption from renal tubules independent of the blood glucose levels [23].

Mesangial cell changes and diabetic nephropathy in hypertensive patient

Earliest lesion observed in an insulin-dependent diabetes mellitus patient is observed as mesangial expansion. Experimental studies suggest that earliest pathological changes in a diabetic patient are enhanced thickness of the glomerular basement and therefore upsurge in the capacity of glomerulus. Persistent matrix growth in the mesangium leads to severe diffused or nodular glomerulosclerosis. Effect of hyperglycemia on the basement membrane is already reported and it is known that non-enzymatic glycosylation of protein like type IV collagen and laminine present in the basement membrane causes the loss of permselectivity on the renal apparatus and thus leading to proteinuria. These advanced end-glycation end product have pertinent influence on the renal mesangium. Binding of AEG with these cells triggers increased synthesis of fibronectin and other mesangial proteins together causing increased basement membrane thickening and therefore precipitation of nephropathy [24].

Contraction of mesangial cells can alter the capillary flow and pressure as they bind together the capillary loops. Since the mesangial cells can react to the vasoactive substance like angiotensin II and endothelin-1, chronic contraction of mesangial cells and thus capillary loops can be observed in the hypertensive diabetic patient who have high amount of circulating vasoactive substances due to various pathological consequences as discussed above [14]. A direct association has also been discovered between hyperglycemia and increased synthesis of local growth factors which causes over proliferation of mesangial cells and thus leads to matrix overproduction and therefore nephropathy. Hypertrophy and inflammatory changes of mesangial cells promoted by local growth factors along with vasopressin and angiotensin II is the main cause of mesangial atherosclerosis which is explained by the presence of foam cells, extracellular matrix material, and presence of unstructured fragments in around 25% of the chronic diabetic patients.

All these factors together leads to glomerulosclerosis in type I along with type II blood sugar sufferers [24].

Role of anti-hypertensive drugs in restricting diabetic nephropathy

The above section clarified how hypertension increases the chances of developing vascular complications like nephropathy in diabetic patients. It is estimated that 35-40% of the diabetic nephropathy patients have history of hypertension. Many studies have thus evaluated the effects of anti-hypertensive drugs in type 1 along with type 2 blood sugar sufferers with nephropathy. Combined findings of all these trials suggest that management and controlling blood pressure less than 140/90 mm Hg in a diabetic patient restricts the further progression of renal diseases like nephropathy. Furthermore, it has also been found that the consequence of antihypertensive drug on reducing the advancement of the blood sugar nephropathy is free of its blood pressure decreasing influence [14].

Initiation of pharmacological therapy for hypertension is recommended when lifestyle modifications like diet control, smoking cessation, reducing alcohol consumption, and including exercise in daily routine fails to control high blood pressure. The five major classes of anti-hypertensive medicines which are presently utilized for the management of diabetic nephropathy are discussed below. These drugs are specifically selected as first-line solitary agent treatment after the findings of large randomised control trial. Each drug class has its own positive effect along with its specific adverse effects [25].

ACE inhibitors

There are no disadvantages associated, in regards to lipid levels and management of hyperglycemia, with the treatment of ACE inhibitors in a diabetic nephropathy patient. Studies suggest that ACE inhibitors are significantly effectual in retarding the development of diabetes nephropathy in a hypertensive diabetic patient. It is suggested that ACE inhibitors act by reducing the glomerular capillary pressure. The extensive pressure on the glomerular apparatus due to renal sclerosis (because of diabetes) and volume overload (because of hypertension) are the main causes of kidney injury and therefore progression of nephropathy. By reducing the glomerular pressure by inhibiting the angiotensin changing enzyme which leads to the synthesis of vasoconstrictive angiotensin II, the drug reduces the chances of further ischemic damage and thus glomerulosclerosis [26].

First major attempt to evaluate the effectiveness of ACE inhibitors in diabetic nephropathy patients was performed in the year 1992. The randomised control trial included 40 patients with chronic history of type 1 blood sugar mellitus along with signs of diabetic nephropathy. The participants were then randomly divided to two intervention groups which were enalapril and metoprolol both combined with furosemide. The results suggested that enalapril was highly effective in improving glomerular filtration rate and proteinuria as compared to metoprolol. It was even perceived that the level of blood pressure reduction in both the sets was not statistically significant [27]. A prospective study by Diabetes Collaborative Group examined the effectiveness of captopril in retarding the advancement of blood sugar nephropathy. The randomised control trial recruited 100 IDDM patients with proteinuria above 500 mg/dl and serum creatinine levels below 2.5 mg/dl. The patients were arbitrarily divide to two sets where one set got captopril treatment while other received different unknown BP lowering agents. The three year follow up study observed that doubling of serum creatinine was observed in only 25 patients receiving captopril in comparison to 43 patients in the other set. It was suggested that captopril minimizes

the peril of serum doubling by 48%. The study drug was also found to be associated with 50 percentile decrease in the rates of collective end facts like mortality, need for dialysis, and requirement for kidney transplantation. Subgroup data analysis indicated that nephrotic-range proteinuria was again observed in captopril group after cessation of the therapy. All the findings thus concluded that along with improving glomerular filtration rate, captopril also reduces the risk of increased serum creatinine and increased proteinuria [28].

While most of the researches for nephropathy control using ACE inhibitors are focused on insulin-reliant blood sugar patients, a five-year research evaluated the drug effect on non-insulin reliant blood sugar mellitus patients. The study observed the consequence of the drug on reducing proteinuria in the NIDDM patients with microalbuminuria. The randomised control trial on 94 patients with initial signs of diabetic nephropathy found that ACE inhibitors were effective in providing long-term stabilisation of serum creatinine as well as albuminuria [29].

A prospective 3-year study on NIDDM patients in a placebo controlled double blind setup concluded that ACE inhibitor enalapril is far more effective in controlling loss of renal function as well as GFR when compared to any other anti-hypertensive drug. Higher rate of GFR loss was seen in the sufferers with extensive proteinuria at baseline in comparison to the sufferers with subclinical proteinuria (Albumin excretion more and less than 300 mg/24hrs respectively). It was also noticed that enalapril was more effective in improving GFR if the patient have subclinical proteinuria. On prolonged treatment it was found that on 7% of the patients treated with enalapril showed advancement in albuminuria in comparison to 21% patients in the control group. All these outcomes recommended that ACE inhibitors especially enalapril must be utilized as a first line cure for the restriction of nephropathy in hypertensive NIDDM patients with or without albuminuria and the drug must not be reserved till clinical albuminuria or proteinuria advances [30].

A meta-regression examination of around 100 controlled and uncontrolled trial for ACE inhibitors in the retardation of nephropathy in diabetes sufferers observed the effect of the drug category on the renal function and proteinuria as compared to the other drugs. Manifold linear deterioration examination of all these studies revealed that ACE inhibitors were highly effective in reducing risk of proteinuria and the effect was independent of BP control, duration of the therapy, form of diabetes, and stage of nephropathy [31].

While the drug category show high effectiveness both for BP control and nephropathy retardation, there are certain significant adverse effects also associated with the long-term use. The major adverse consequence of ACE inhibitors is that they accelerate the development of renal deficiency in the patients with two-sided renal artery stenosis which is observed in many diabetic patients. In certain conditions where the filtration pressure is dependent on the angiotensin II, the use of these drugs may lead to extensive fall in glomerular filtration rates. Such complications are very probable to transpire in the case of stenosis of both the renal arteries due to arteromatous plaques or in case of severe congestive cardiac failure. ACE inhibitors might also induce hyperkalemia especially in the patients having low GFR or the patients with impaired aldosterone action which may lead to severe cardiac consequences. Profound caution should be taken while starting ACE inhibitor treatment in the patients already getting diuretic as the combination may lead to hypotension and extensive decline in renal function [32].

Calcium antagonist

Different studies related to the action of calcium adversaries in the management of diabetic renal ailments provided conflicting views. The study by Melbourne Diabetic Nephropathy board associated the ACE inhibitor perindopril with calcium channel blocker nifedipin. The primary outcomes observed were reduction in albuminuria and blood pressure. All the 43 diabetic patients selected were having chronic microalbuminuria. Following a 12-month therapy session, the researchers perceived that both the drugs were similarly effective in minimizing both the blood pressure and albuminuria. But, a 24 month follow up of the same regime showed that proteinuria and albuminuria returned back to the baseline levels in the nifedipin group but the levels remained constantly low for the ACE inhibitor group [33].

It is also advocated that a mixture of calcium channel blocker and ACE inhibitors may provide better proteinuria reduction as well as better restriction of morphological changes leading to nephropathy. A study observed these effects of calcium channel blockers and ACE inhibitor combination. The NIDDM patients treated with the combination showed greatest decrease in albuminuria as compared to treatment with any of the category alone [33].

Thiazide diuretics

Low dose thiazide diuretics are considered beneficial in regulating blood pressure in diabetes sufferers. Randomised control trial with large subject population suggests that thiazide diuretics are essentially helpful in reducing morbidity and mortality due to cardiac complications in diabetic patients. However, improper or high dose of thiazide diuretics can alter the carbohydrate metabolism and can induce hypokalemia, hyperuricemia and hypomagnesemia. Since majority of the hypertensive patients experience volume overload they requires treatment with diuretics. Thus it is suggested that using thiazide diuretics to manage hypertension must be done carefully in diabetic patients and the dose must not exceed above 25 mg per day. Since short-term dyslipidaemia is also one of the consequences of thiazide diuretics, the drug could lead to renal atherosclerosis and therefore must always be used in combination with ACE inhibitors and in low doses [34].

β -Blockers

There are many concerns related to the use of beta blockers for the management of hypertension in diabetic sufferers. Beta blockers adversely affect the glucose and lipid metabolism and therefore may lead to renal morphological changes due to sustained hyperglycemia. Beta-blockers can pose high risk to insulin treated diabetic patients as the drugs reduces the patients' awareness about hypoglycaemia and therefore treatment of hypoglycaemia is avoided which in turn can lead to severe metabolic consequences. The drug blunts the catecholamine response to hypoglycaemia like reflex tachycardia. Blunting of such hypoglycaemic symptoms prolongs the recovery from the condition and may in extreme cases may lead to central nervous system damage. The drug may aggravate the compromised condition of peripheral vasculature by reducing blood flow and increase claudication and vasospasm. The hyperglycaemic effect of beta-blockers is synergised when they are given in combination of diuretics. Thus it is recommended that beta-blockers must not be used in the treatment of hypertension in diabetic patient except special circumstances like occurrence of angina pectoris and immediately following myocardial infarction [32].

α 1-Blockers

α 1-Blockers are advised for the cure of hypertension in diabetic patient

since they are effective and lack adverse effect like alteration of lipid and glucose metabolism. In fact the drugs are considered to have positive effect on lipid profile of such patients. These agents also do not produce or enhance sexual dysfunction but allows improvement of sexual function when used instead of central sympatholytic agents. No reports are available which suggests that peripheral alpha-1 blockers lead to orthostatic hypotension which is a common adverse effect of centrally acting sympatholytic. Use of centrally acting sympatholytic agents like clonidine, methyldopa, etc. for the cure of high tension in blood sugar patients requires knowledge of both its advantages and disadvantages. While advantages of the drugs include no negative effect on lipid profile and absence of disturbed glucose metabolism and thus hyperglycemia. On the other hand the main disadvantages are aggravation of orthostatic hypotension and sexual dysfunction. Although the adverse effects are few but are highly putative and therefore centrally acting sympatholytic drugs are never a choice of antihypertensive drugs in a diabetic patient [35].

Future Considerations

Extensive research is still required to identify most appropriate antihypertensive drug which can provide prominent blood pressure regulator and avert development of renal damage with little or no adverse effects. While extensive research is available which explains the effectiveness of ACE inhibitors in stoppage of blood sugar nephropathy in IDDM patient but still there is dearth of research which suggest similar action of the drug category in NIDDM patients. Renoprotective effects of calcium channel blockers is yet debated and therefore research is required to identify the exact mechanism by which calcium channel blockers may provide beneficial effect in case of diabetic nephropathy patients. Considering the underlying pathology which leads to development of vascular damage and remodelling in a diabetic patient, different drug categories like HMG CoA reductase inhibitors, acarbose, and aldose reductase inhibitors must be evaluated in long-term clinical trials. Effect of these drugs in improving GFR and reducing anatomic changes must be assessed. Protein restriction is highly recommended for diabetic patients showing signs of proteinuria; however extensive research is required to identify the exact effectiveness of this intervention in type 1 along with type 2 diabetes sufferers [36].

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