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Effects Of GLP-1 Analogues, DPP-4 Inhibitors And SGLT2 Inhibitors On The Renal System

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ABSTRACT

Introduction: In order to prevent diabetic nephropathy (DN) that affects an estimated 30-45% of patients with diabetes mellitus type 2, a new therapeutic alternatives including the analogues of GLP-1, inhibitors of DPP-4 and the inhibitors of SGLT2 which seek to reduce the morbi-mortality have been developed. **Methods:** Meta-analysis of new experimental studies in rats and observational in patients with diabetes who are at risk of suffering from DN. **Results:** improvement in albuminuria achieved with DPP-4 and SGLT2 inhibitors suggests that these antidiabetic drugs can potentially provide kidney benefits beyond their glucose lowering effects. The use of the GLP1 analogues still remains controversial. **Discussion:** There are pathophysiological mechanisms by which recipients of the drugs studied decreasing or inhibiting its therapeutic action is alter, the discussion focuses on determining what conditions make it difficult to function. **Conclusion:** The optimal treatment and prevention of DN requires an early intensive and multifactorial approach to the kidney risk factors. Recent studies indicate that these hypoglycemic have promising effects on the renal system, because they help prevent the progression of glomerular damage in diabetic patients. The regular monitoring of renal function is fundamental to any progression of the disease and adjustment of treatment.

Keywords: Diabetes, diabetic nephropathy, DPP4, SGLT2, GLP1.

Introduction

Diabetic nephropathy (ND), carries a heavy burden of economic and clinical, since it is present in up to 40% of patients with Diabetes Mellitus type 2. Modifiable risk factors are key to the DN and include hypertension, Hyperglycemia, Hyperlipidemia, anemia, albuminuria and in addition factors such as obesity and smoking. Early identification of risk factors is key to early therapeutic intervention and this can potentially prevent or slow the decline in renal function in patients with Diabetes Mellitus type 2. The main objective of this article is to discuss the potential improvement of the prevention and treatment of DN, including the use of drugs that offer direct protection of organ damage associated with diabetes as well as risk factor control. (Guntram Schernthaner, 2014)

Analogs of GLP-1

Peptide glucagon - 1 (GLP- 1) is a secreted incretin hormone from L enteroendocrine cells (Young Min Cho, 2013) is released in the intestine in response to fat or carbohydrate and contributes to the feedback control negative of blood glucose by stimulating insulin secretion, inhibition of glucagon, and slowing gastric emptying. GLP-1 receptor (GLP-1R) is also expressed in the proximal tubule, and possibly kidney elsewhere. Once the GLP- 1 reaches the circulation , it has a half- life of only 2 minutes due to rapid degradation by the enzyme dipeptidyl peptidase -4 (DPP -4). As a result of these activities glucose reduction and intense efforts has led to the use of GLP- 1 for the treatment of diabetes (Scott C. Thomson, 2012).

DPP-4 Inhibitors

The concentration of GLP-1 is decreased in Type 2 Diabetes Mellitus, but its action is intact, so that to give GLP-1 infusion in the effects described above are obtained, as in the healthy individual. What happens in the DM2 is a deficit in the amount of GLP-1, not in function. The effects of GLP-1 on insulin and glucagon has been dependent glucose DM2, so that with hyperglycemia (after meals with Carbohydrates) GLP-1 stimulates insulin production and suppresses glucagon, and when glucose levels are normal, insulin secretion decreases and glucagon no longer suppressed. In contrast, sulfonylureas act independently of glucose levels in blood, thus having a risk of causing hypoglycemia, which is something that would not occur in the monotherapy with incretins (or cancellers of enzyme inhibitor such as Sitagliptin), so its effect is more physiological. Incretins have a very short half-life and is rapidly degraded by the Di-peptidyl peptidase-4 (DPP-4) and by enzyme inhibitors of this enzyme, it is possible to keep these hormones longer acting. (Timo Rieg, 2014)

SGLT2 Inhibitors

Inhibitors dependent glucose transporter sodium (SGLT) -2, a new diabetes strategy, point to the renal proximal tubules to block the reabsorption of glucose, thereby improving urinary excretion of glucose and anti-hyperglycemic effects confer. They are indicated for use in people with type 2

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diabetes (as long as renal function is moderate at least) and are under clinical investigation as an adjunct to exogenous insulin in type 1 diabetes clinical studies with SGLT2 inhibitors have been reported fasting plasma glucose reductions and glucose (HbA1C) levels of hemoglobin (0.7 to 0.8%) compared to placebo and other strategies hypoglycemic and a reduction in cardiovascular mortality in patients with type 2 diabetes and high cardiovascular risk . (Linda A. Gallo 2016) Among the new therapies on the horizon, inhibitors of sodium-glucose cotransporter 2 (SGLT2) look promising, and there are a number of ongoing phase II and III clinical trials with a variety of these compounds. SGLT2 is almost exclusively expressed in renal proximal tubules and represents 90% of the renal glucose reabsorption. SGLT2 inhibitors work independently of insulin and lead to a negative energy balance by enhanced glucose excretion Urinary. This makes it possible mechanically to this class of drugs to reduce glucose levels without causing hypoglycemia and weight gain. However, the side effect profile has not yet been elucidated ongoing Phase III trials, and must be shown to be safe from a renal and cardiovascular perspective for these compounds to meet current regulatory requirements for new diabetes treatment (Sunil Nair, 2011).

Table 1.

	Function
Analogs Of GLP-1	Stimulation of insulin secretion, inhibition of glucagon, and slow gastric emptying.
DPP-4 Inhibitors	Inhibitors of this enzyme are responsible for degrade GLP -1 produced by the intestine.
SGLT2 Inhibitors	They point to the renal proximal tubules to block the reabsorption of glucose, urinary excretion of Improving thereby glucose and confer anti-hyperglycemic effects.

Materials And Methods

Used 20 bibliographical reviews on research of the drugs in question therefore in carrying out each of them several methodologies were used emphasizing the following:

Experiments with animal

They were conducted with rats aged between 6 weeks and mice males of ages up to 9 weeks. The animals were housed in individual cages in an environment of temperature and light-controlled and had access to water. It was induced in rats by a single intravenous injection of IgG monoclonal mouse (1.2 mg / kg).

Use of Immunohistochemistry methods

The following primary antibodies were used:

- Monoclonal mouse anti-CD68
- Monoclonal of mouse anti-CD163

Renal histology analysis

Tissues were fixed in formalin and paraffin. Three sections-micrometre were dyed with reactive periodic acid-Schiff and contrast with hematoxylin. Quantification of renal histology was performed as previously described using the following system:

0 = normal appearance.
1 = mesangial expansion and hypercellularity.
2 = microaneurysms, necrosis, capsular hemorrhage, or array, or cellular half-moons. Quantitative analyses were carried out in a blind way.

Another study was an arm parallel, randomized, multicenter, double-blind, 24 weeks of the study carried out in 87 centres in Brazil and the United States. Patients with diabetes type 2, naive or treated with any medication to lower the glucose, that had a control Glycemic inappropriate (HbA1c drugs 6, 5-10, 0% [48-86 mmol / mol]) and a rate of filtration glomerular estimated < 30 ml min^{-1} [1.73 $m]^{-2}$ were assigned to the random (through the voice response interactive) to Vildagliptin 50 mg per day or 25 mg of Sitagliptin per day.

These doses are recommended in this population of patients and considered of maximum efficiency. The participants, the researchers and the sponsor were blinded to the assignment of groups. The effectiveness variables included changes in HbA1c of glucose in fasting and plasma in fasting (FPG) in all the visits and the primary endpoint was safety evaluation of treatment emergent adverse events.

In total, 148 patients were assigned at random, 83 of Vildagliptin, Sitagliptin 65. All patients were analyzed. After 24 weeks, the half adjustment change was of 0.54% with Vildagliptin and 0.56% with Sitagliptin, then we can see that both treatments were well tolerated with profiles of security similar.

In another study of Cotransportadores of sodium glucose were used and compared with mice. All mice were fed a diet of low glucose, protein, fat, fibre, starch, sugar. To prevent too much absorption of glucose / galactose and subsequent diarrhea due to the absence of SGLT1. Mice were housed in the animal room with free access to running water and during a 12 h light-dark cycle (Glastras *et al*., 2016).

- Glucosuric acute and chronic responses selective SGLT2 inhibition in Sglt1-/- and WT mice.
- Empagliflozin is a selective inhibitor of SGLT2 with CI.

SGLT2 is highly selective in humans and mice were used as a pharmacological tool to inhibit SGLT2.

Three series of studies were performed with the following:

1. First tried mice Sglt1 by oral probe with Empagliflozin (0.1 - 30 mg/kg) together with load of water to facilitate subsequent quantitative urine collection metabolic cages about 3h.
2. Secondly, mice were treated with Empagliflozin (300 mg/kg diet) for three weeks, the body weight, the proportions of glucose/creatinine, urine, blood glucose levels, were measured in the food and fluid intake. Food

and fluid intake was determined while the mice were maintained in their regular cages. Urine was obtained at the same time of day the mice to cause urination reflects, for glucose measurements matched, blood was collected by clipping tail immediately after the collection of urine in awake mice.

3. Third, after 3 weeks of treatment with Empagliflozin inulin clearance studies were conducted to determine the filtration rate (GFR) glomerular, filtered glucose, urinary excretion of glucose (UGE) and FGR terminal anesthesia.

Briefly, the mice were anesthetized with thiobutabarbital (100 mg/kg ip, 2 µl/g weight of body; Sigma - Aldrich, St. Louis, MO) and ketamine (100 mg/kg im, 2 µl/g weight of body; Butler, OH). The jugular vein was canulada for continuous infusion of 2.25% bovine serum albumin in 0.85% NaCl at a speed of 0.4 ml·hde·30-$^{-1}$-$^{-1}$ g body weight. For two kidneys evaluation of GFR by inulin clearance, [^{3}H] inulin has been added to the infusion to deliver 5 µCi·h-$^{-1}$-$^{-1}$ ·30 g body weight the urinary excretion of glucose and [^{3}H] inulin was evaluated by quantitative collection through a catheter bladder in periods of 30 min. Blood samples (50µl) were drawn half way through each period of an arterial catheter, which was also used to monitor blood pressure and heart rate. The concentrations of [^{3}H] inulin in the plasma and urine were measured by Liquid Scintillation counting.

Analysis of blood and urine

In the awake mice blood glucose was determined using a glucometer. Glucose in plasma in the studies of space and all the glucose in urine is determined by the method of hexokinase / glucose-6-phosphate dehydrogenase. Total concentrations of Empagliflozin in plasma were determined by liquid chromatography tandem mass spectrometry. It was found that the fractional protein binding average Empagliflozin in mouse plasma is constant over a wide range.

In another study have been conducted a retrospective, longitudinal, observational study in patients, the kidney transplant patient with diabetes who initiated treatment with inhibitors of DPP-4 (Vildagliptin, sitagliptin, and linagliptin) after transplantation were enrolled in this study. All the receivers of translation of the knowledge, both in the hospital received therapy of maintenance triple that is composed of Cyclosporine, Mycophenolate of mofetil or azathioprine and corticosteroids. All of the study patients survived > 12 months after transplantation.

Materials

- Males rats of between 6 to 9 weeks of age.
- Inhibitors of the DPP-4 (Vildagliptin, the sitagliptin, and linagliptin).
- Renal histological analysis.
- Analysis of blood and urine.

Results

DPP-4 Inhibitors

DPP-4 is expressed and is found in many cell types, including endothelial cells in multiple vascular beds, making the enzyme highly accessible to peptide substrates circulating through the intestine, liver, lung and kidney. Some researchers have shown that increasing activity of DPP-4 in the kidney or urine is a characteristic of glomerular diseases.

Incretins are a group of metabolic hormones that stimulate decreased levels of blood glucose, either increasing insulin release or reducing gastrointestinal absorption. The prototypical incretins are GLP-1 and GIP hormones, both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4. Therefore, DPP4 is a drug for the treatment of Diabetes Type 2.

There are two types of DPP-4 used in the clinic: mimetics dipeptide structure and non peptidomimetics. The first type includes sitagliptin (approved by the FDA in 2006), Vildagliptin (approved by the European Medicines Agency in 2007), and Saxagliptin (approved by the FDA in 2009), while non-peptide mimetics include Linagliptin (FDA approved in 2011) and Alogliptin (approved by the FDA in 2013). (Kirby *et al*, 2010)

These are all small molecules that are quickly absorbed after oral dosage, resulting in an inhibition greater than 80% of the activity of DPP-4 over a period of 24h.

Effects of DPP-4: The main beneficial effects of inhibitors of DPP-4inhibitors in diseases such as diabetes found in different studies, are the following: a) significantly reduced fasting plasma glucose and HbA1c levels in a study of 4 weeks, b) The efficacy of DPP-4 inhibitors in reducing glycaemia is weaker compared sulfonylureas, insulin, and thiazolidinediones, but are significantly better tolerated and do not produce weight gain, c) Linagliptin decreases urinary albumin excretion in patients with type 2 diabetes after 24 weeks of treatment, d) oral antidiabetic monotherapy was significantly associated with a lower probability of decreased levels of HbA1c, e) treatment with inhibitors of DPP-4 decreased by 16% the risk of episodes of kidney disease.

Furthermore the following are the effects of inhibitors of DPP-4 on the: a) can prevent renal fibrosis, b) can improve diabetic nephropathy and reduce overproduction of TGF-?1, c) it was shown that inhibitors DPP-4 significantly attenuate the toxic effect of Indoxyl sulfate (IS). The IS accumulates in serum due to impaired renal clearance, it has been shown to cause overproduction of ROS contribute to the progression of renal injury in chronic conditions leads to a pathological fibrosis. (Taki *et al*, 2006). d) Treatment with DPP-4 attenuates renal injury and improves acute and chronic injury, e) prevented progression of microalbuminuria in patients with renal insufficiency of moderate to severe, f) In patients who are undergoing chemotherapies inhibitors of DPP-4 nephrotoxicity and improve ischaemia-induced injury cisplatin g) was also observed to reduce macrophage infiltration thus improve the glomerular injury and proteinuria in a model of glomerulonephritis.

In Table 2, the classification of the types of inhibitors of DPP-4 and named in the studies is noted and is described in each different beneficial and no beneficial effects.

Effects of DPP-4 in patients with renal transplantation and diabetes

In this study treatment began with inhibitors of DPP-4 to 65 patients with diabetes who underwent a kidney transplant.

The inhibitors of DPP-4 used in this study were Vildagliptin in 17 patients, 28 patients Sitagliptin and linagliptin in 20 patients. Among these, the effects produced which was more

beneficial for these patients were compared. The age of these patients ranged from 42 to 61, males predominated. Doses used were: for Vildagliptin and Sitagliptin 50 mg 1 time per day and 100 mg Linagliptin.

The results after 3 months of treatment were analyzed and it was found that: HbA1c, glucose and glomerular filtration rate were significantly reduced in the Linagliptin group compared to other group's inhibitors DPP-4. Patients in the sitagliptin group showed a higher concentration of Cyclosporine (immunosuppressant drug used in organ transplantation) serum.

Linagliptin showed better efficacy in treatment with inhibitors of DPP-4 in patients with type 2 diabetes and kidney transplantation. It also indicates that inhibitors of DPP-4 have a protective effect to the survival of pancreatic β cells and preserving or even improving their function may be beneficial for glycemic control in patients with organ transplants. (Hecking *et al*, 2013).

Table 2: Classification of the different types of inhibitors of DPP-4 and its effects

DPP-4 Inhibitors	Beneficial Effects	No Beneficial Effects
Saxagliptina	-Reduce The progression of diabetic nephropathy -Reduces HbA1c levels at 1 year -Modest but significant improvement in glycemic control. -Prevented the progression of microalbuminuria in patients with renal insufficiency of moderate to severe	-At least one adverse event occurred in 152 (88%) of patients treated with IR.
Alogliptina	-Reduces infiltration of macrophages in the injured kidney	-The results were not significant to the decline in glomerular injury and proteinuria
Vildagliptina	-50 mg dose administered once daily -It decreased plasma glucose fasting -HbA1c levels decreased	-The peripheral edema appeared as an adverse effect
Sitagliptina	-25 mg dose administered once daily Reduces HbA1c levels	-Increase levels of FPG -Hipoglucemia It reported more frequently -He reported as adverse effect peripheral edema
Linagliptina	-Reduced significantly the risk of kidney disease episodes 16% -Decreases The progression of renal disease in patients with type 2 diabetes. -You can reduce urinary albumin excretion, renal fibrosis, oxidative stress and inflammation	-Episodes of hypotension occurred in 0.3% of participants in the linagliptin group.

Analogs of GLP-1

GLP-1 is an incretin hormone secreted by the small intestine in response to nutrient ingestion and degraded by the dipeptidyl peptidase IV (DPP-IV). GLP-1 acts through receptor GLP-1, a receptor protein G- coupled, expressed not only in the gastrointestinal tract, but also in the nervous system, heart, vascular smooth muscle, proximal tubules and glomeruli of the kidney. GLP-1 increases insulin secretion from the pancreas ?-cells and reduces glucagon release cell-?. GLP-1 also decreased gastric motility and emptying and increases satiety. (Ryan *et al,* 2011).

Receptor agonists of GLP-1 effects extend endogenous GLP-1 resist enzymatic degradation. Therefore are injectable drugs used to treat type 2 DM.

The first generation of GLP-1 which was the development of short-acting: usually requires injection twice a day (for example, exenatide). The second generation of GLP-1 are long-acting, with a duration of sufficient activity to a regimen of injections once a day (eg Liraglutide). The third generation extend analogous action of GLP-1 with sustained action which requires a dosing regimen ranging from injection once a month, once a week (for example, the exenatide LAR-or weekly exenatide) (table 3). (Salvador & Gaztambide, 2014).

Exenatide: Eliminated by the kidneys, mean half-life of 3-4 hours. Among the effects of exenatide in renal function include the following: a) decreases the transforming growth factor-beta1 (TGF -?1) this is an important fibrogenic growth factor for the pathogenesis of glomerulosclerosis and interstitial fibrosis, and inducing collagen synthesis and matrix and expression of growth factor tissue, b) resulted in improving glomerular hyperfiltration, glomerular hypertrophy, albuminuria and expansion of mesangial matrix, c) improved endothelial function of renal arteries of hypertensive patients, d) Exenatide resulted in a significant reduction in body mass index (BMI), e) Similar reductions were observed in fasting glucose and HbA1c.

AKI induced exenatide: There are a number of case reports exenatide association with the development of acute renal injury. Effects of GLP-1 and natriuresis and possible decreased renal perfusion may also play a role in fluid loss and impaired renal function. A kidney biopsy, which was performed in a patient revealed ischemic glomeruli with moderate to severe interstitial fibrosis and early diabetic nephropathy.

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Exenatide should not be administered in patients with chronic or severe renal impairment.

Liraglutide: It has a half-life of 11 to 15 hours. Effects of Liraglutide: a) reduced levels of HbA1c levels and fasting glucose for fed with type 2 diabetes by improving insulin secretion, suppressing the secretion of postprandial glucagon patients, delaying emptying gastric, and increased satiety, b) normalizes the excretion of albumin in urine and oxidative stress markers and expression of TGF -?1 and fibronectin in renal tissue.

Some adverse effects that in most cases can be mild but in other cases these effects may be potential risks of chronicity were evident. Adverse effects are described in Table 3. (Salvador & Gaztambide, 2014).

In general, agonists GLP-1 receptor appear to improve markers histological changes and diabetic nephropathy. These effects appear promising for the treatment of patients with DM type 2. However, it should be mentioned that most of the evidence is based on animal studies and studies of the effects on human physiology should be done with caution.

SGLT2 inhibitors

SGLT2 inhibitors block the reabsorption of glucose filtrated by SGLT2 inhibition, primary glucose transporter for proximal tubular cell the (PTC), leads to glycosuria and decreased serum glucose. Are promising agents (not yet on the market) used to achieve glycemic control in type 2 diabetes who have the added advantage of not promoting hyperinsulinemia, weight gain or inducing hypoglycemia. Its method of action is to block the entry of glucose for the proximal tubular cells of the kidney.

Transporter inhibitors CO2 sodium / glucose (SGLT2 inhibitors) are promising agents (not yet on the market) used to achieve glycemic control in type 2 having the added advantage of not promoting hyperinsulinemia diabetes, weight gain or inducing hypoglycemia. Its method of action is to block the entry of glucose for the proximal tubular cells of the kidney, a process known to fully participate in the development of diabetic nephropathy. (Ghosh *et al*, 2011).

Table 3: Classification of GLP-1 and its adverse effects

Analogs GLP-1	Characteristics	Average Life	Adverse Effects
Exenatida	-First generation -Action short -Injection twice daily	3-4 hours.	**Mild:** nauseated vomiting Diarrhea **Serious:** Development of acute pancreatitis, chronic pancreatitis, pancreatic cancer and thyroid cancer.
Liraglutida	-Second generation -Long-acting -Injections once a day	11 to 15 hours	
Exenatida LAR-o Exenatida semanal	-Third generation -Sustained action -Dosage ranging from injection once a month, once a week).	2 weeks	

Dependent glucose transporters sodium (SGLT), located at the apical side of the proximal tubule cell, are capable of transporting glucose into the cell against a concentration gradient by glucose transport while sodium. A sodium concentration gradient is by the Na-K-adenosine triphosphatase (Na-K-ATPase) pump located for the basolateral membrane.

The foundation of SGLT2 inhibitors as therapeutic agents, therefore, is that interference with the major glucose transporters in the proximal tubule improve glucose excretion in the urine and glycosuria leading to improved glycemic thereby control.

In patients with type 1 DM attenuates renal hyperfiltration, probably by affecting tubular glomerular feedback mechanisms. The side effect profile has not yet been elucidated and will be proven to be safe from a renal and cardiovascular perspective.

Clinical studies are needed to determine whether SGLT2 inhibitors offer greater renal protection compared with other oral hypoglycemic agents used to treat type 2 diabetes mellitus.

Discussion

In this review, we conducted an exhaustive evaluation of the effects of certain hypoglycemiants (GLP-1 Analogs, DDP-4 inhibitors and SGLT2 inhibitors) on the renal system, based on data studies in animals and normal humans and diabetic people, with or without some degree of renal damage.

Effects of glp-1 analogues in the renal system

Previously, it was shown that protein C kinase, B isoform (PKC-B), increases the proinflammatory effects of angiotensin II (Ang II) causing an increase of the plasminogen activator - 1 (PAI-1) in glomerular endothelial cells and can also inhibit the protective actions of GLP-1 by reducing the expression of their receptors in endothelial cells; currently Mima., *et al* 2012 show that endothelial dysfunction in diabetic patients is given by overexpression of PKC-B in endothelial cells induced by hyperglycemia, and analogues GLP-1 inhibit the signaling of Ang II which suggests that effective therapeutic agents can be designed to improve the GLP-1 receptors in the endothelium, for a possible prevention of glomerular endothelial dysfuntion and slow the progression of diabetic nephropathy.

Effects of DPP-4 inhibitors in the renal system

The IDPP-4 improve renal injury models of animals with diabetic nephropathy, by suppressing macrophage infiltration through the GLP-1 signaling; but the present results suggest that the alopgliptina reduces macrophage infiltration in glomerular injury but not significantly in models with rats with nephritis, although there is a tendency to improve proteinuria (Higashijima., *et al* 2015).

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Cooper, *et al* 2015 reported that his clinical trial of randomized studies in diabetic patients with CKD that Linagliptin more than being a IDPP-4 that does not require dose adjustment; it is not associated with increased renal risk, whereas reducing the risk compared to placebo by 16%, at the same time it is not associated with risk of hypotension or hyperkalemia, still in combination with a RAAS inhibitor.

Hyperglycemia is associated with adverse outcomes in diabetic patients with renal transplantation, including graft loss and mortality, also we should be aware that these patients receive cyclosporine which is metabolized by the cytochrome P450 system; previous studies showed that IDPP-4 succeeded in reducing HbA1c, but these drugs have metabolism and independent variable excretion for each one, this difficult to choose one of them in this group of patients, however thanks to current studies, it is possible to determine that within this group of drugs for the require conditions the best option is linagliptin because it significantly reduces HbA1c levels, its elimination is primarily by the feces (84.7%) and by the kidney is only 5.4%, also it has a minimal effect on maximum concentration of cyclosporine (Bae., *et al* 2016).

No past data have been obtained comparing the effects between Vildagliptin and Sitagliptin, in diabetic patients with CKD; but a current study suggests that both drugs are well tolerated in these patients, with a renal excretion without metabolized 20 and 80% respectively, values of HbA1c ? 6.5% can be achieve with Vildagliptin in a larger group than with Sitagliptin (Kothny., *et al* 2015).

Effects of SGLT-2 inhibitors in the renal system

Data showed that in diabetic animal models along proximal tubule segments the inhibition of glucose SGLT-2 cotransporter affects the oxygen consumption (QO2) on an average by 30 - 60%, with the current results it is suggested that value varies in rise of referential values between 9 to 12% and in turn this blockade reduces the active transport of Na ++ (TNA ++), but also shows that these effects are offset by an increase in transport mediated by SGLT- 1 cotransporter and Na ++ / H + exchangers (Layton., *et al* 2015).

In turn there is evidence that the inhibition of SGLT-2 (Empaglifozin), produces a saturation of SGLT-1 cotransporters favoring the renal reabsorption of glucose, the current results suggest that in kidneys of diabetic mice untreated the SGLT -1 cotransporter is responsible for only 3% of reabsorption of filtered glucose and pharmacological inhibition of SGLT-2 produces a compensatory increase over the reference value in that cotransporter limiting lower blood glucose levels in Diabetes Mellitus (Rieg., *et al* 2012).

The inhibition of SGLT-2 on intraglomerular hyperfiltration and hypertension is another kidney effect to analize, animal studies revealed that indeed both acute and chronic blockade of SGLT-2 cotransporter meets these effects being practically helpful for protection in the progression of CKD related to Diabetes Mellitus, unfortunately it does not have data on human studies; but current results are controversial because, Zhang., *et al* 2013 shows that in animal models with CKD nondiabetic, the inhibition of SGLT-2 provides no evidence of renal protection, while Cherney., *et al* 2015 reports that treatment with empaglifozin in patients with diabetes Type 1 can reduce hyperfiltration, also improve glycemic control being involved its use favorably in prevention for the beginning and progression of diabetic nephropathy.

Conclusion

This group of drugs improves significantly the action, as regards diabetes type II, the analogues of GLP-1 stimulating the secretion of insulin and in turn, the inhibitors of DPP-4 blocking this enzyme avoiding destruction to the GLP-1, decreasing the overload of glucose. At same time, the inhibitors of SGLT2 Act in the kidney by inhibiting the absorption of glucose from the tubules proximal and favoring it output of the same by urine improving the quality of life of the patients. The primary assessment was of much efficiency on the time of the application of the drugs in animals, in this case mice, we can see that the 3 treatments were well tolerated and of great efficiency. DPP-4 inhibitors analyzed at different revisions, bibliographic, among the main and most studied are Alogliptina, Vildagliptin, Sitagliptin, Saxagliptin and Linagliptin which showed a positive effects and renoprotective in diseases such as the Diabetes type 2 and Renal failure. Although the same effect is observed of not so beneficial of which the main and more frequent was the hypoglycemia. So we can say that DPP-4 inhibitors are drugs that help to control Glycemic and protection of kidney in patients with Diabetes and associated disorders.

In addition, recent studies suggest that hypoglycemic have promising effects on the renal system, because they help prevent the progression of glomerular damage in diabetic patients, which as we know is the main cause of decreased glomerular filtration rate that can progress to nephropathy terminal, however it must be stressed that because many of the studies were conducted in animals, raised the necessity to continue research in this group of patients at high risk of kidney damage. (Sen Shi, *et al.*, 2016)

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