CENTRE OF PREVENTIVE MEDICINE
THIRD FACULTY OF MEDICINE CHARLES UNIVERSITY
PRAGUE

DIPLOMA WORK

LOWER URINARY TRACT DYSFUNCTIONS IN PATIENTS WITH DIABETES MELLITUS

WRITTEN BY

ARNFINN OSDAL

SUPERVISER

Doc.ZACHOVAL

DEPARTMENT OF UROLOGY
THOMAYER HOSPITAL
PRAGUE

TABLE OF CONTENT **PAGE**

TERMINOLOGY LIST

ACTH – adrenocorticotropic hormone

ADA – american diabetic association

ALC – acetyl L- carnitine

BOO – bladder outflow obstruction

BPH – benign prostatic hyperplasia

DAN – diabetic autonomic neuropathy

DBD – diabetic bladder dysfunction

DCCT – diabetes clinical control trial

DM – diabetes mellitus

DN – diabetic neuropathy

DPP – diabetes prevention program

DSD – detrusor sphincter dyssynergia

EUA – european urologic association

GAD – glutamic acid decarboxylase

GIT – gastrointestinal tract

HLA – human leukocyte antigen

ICA – islet cell antibodies

ICS – international continence society

IGT – impaired glucose tolerance

LADA – latent autoimmune diabetes of adults

LMN – lower motor neuron

LUT – lower urinary tract

LUTD – lower urinary tract dysfunction

LUTS – lower urinary tract symptoms

MODY – maturity onset diabetes of the young

NLUTD – neurogenic lower urinary tract dysfunction

NO – nitric oxide

PKC – protein kinase C

PNS – peripheral nervous system

SSRI – selective serotonin reuptake inhibitor

STZ – streptozotocin

TCA – tricyclic antidepressives

UI – urinary incontinence

UMN – upper motor neuron

ABSTRACT

Diabetes mellitus (DM) is a endocrine metabolic disorder that is associated with many complications and lower urinary tract dysfunction (LUTD) is one of them. In addition LUTD can be caused by many other disorders and sometimes it can be difficult to isolate the cause. Incidence of diabetes is increasing and prevalence is expected to increase worldwide to 300 million people in 2025. The most important causes for diabetes and lower urinary tract abnormalities are diabetic neuropathy caused by hyperglycaemia. Approximately 50% of diabetic patients develop some form of neuropathy. Diabetes can cause LUTD many ways and research have shown many possible mechanisms involved. Among the suggested mechanisms are up-regulation of muscarinic receptors, smooth muscle hypertrophy, increase in myosin light chain phosphorylation and changes of certain calcium sensitive potassium-channels (MaxiK). The increasing knowledge of pathophysiology and pathogenesis of LUTD made it necessary with a new approach to patients, terminology changes, better definitions and classifications. Among the contributors is European urologic association (EUA).

The importance of preventive measures and good treatment in diabetes can not be underestimated. Their role has an increasing importance today and for the future because of its negative impact on human health with decreased life quality, increased morbidity and reduced life expectancy. DM type-2 is 9 times more prevalent than DM type-1. DM-2 is connected with obesity, hypertension and dyslipidemia. Prevention and treatment differs between the two types of DM due to their etiology. DM-1 has a stronger genetic association than DM-2, this makes the latter easier to prevent and treat.

1.0. INTRODUCTION:

Diabetes and lower urinary tract dysfunction are two separate entities that often coexist. Diabetes is a very common disorder which is increasing in prevalence. It has significant impact on human health, and among the complications is LUTD. The most common cause is diabetic neuropathy, and this will be described in this assay along with other hypotheses for diabetes and LUTD. Additionally the importance of preventive measures and treatment of both diabetes and lower urinary tract dysfunction are described.

2.0. DIABETES MELLITUS (DM)

Diabetes mellitus is a endocrine metabolic disorder characterized hyperglycaemia, relative insulin deficiency, insufficient action of insulin or a combination [1]. Complications of diabetes can be acute or chronic[2]. Commonly it decreases life quality and leads to earlier

death from its complications. Globally it is a growing problem, and it is estimates that the prevalence will increase from approximately 135 millions in 1995 to 300millions in 2025 [3, 4]. DM is diagnosed when fasting blood glucose is above 6.9 mmol/l or 2 hours glucose tolerance test is above 11.1 mmol/l[1].

2.1. TYPES OF DIABETES MELLITUS

Diabetes is sub-classified into more types. But generally DM can be primary or secondary. Most cases are primary. Epidemiologically Diabetes type 1 (insulin dependent diabetes) and diabetes type 2 (non insulin dependent diabetes) are distinct types, but clinically it can be difficult to differentiate them [5]. It also exist some variations of these two main types. Latent autoimmune diabetes of adults (LADA), is a subclass of type 1 DM. Maturity onset diabetes of the Young (MODY), is a subclass of type 2 DM[6]. These two are much rarer than the main types.

2.1.1. DIABETES TYPE 1 (DM-1)

Epidemiology

Type 1-diabetes may occur any age, but usually affects younger people with symptoms debut before 30 year of age and a peak incidence around puberty[4]. LADA has a slower course and onset is later in life and may mimic DM-2 [6]. DM-1 is most prevalent in northern Europe. In general there is a North –south gradient in incidence of the disease, with highest incidence in Finland (1-1.5%) and decreasing incidence in the southerly and tropical regions[7].

Etiology

DM-1 is multifactorial autoimmune disease[5]. It belongs to a family of Human Leukocyte Antigen (HLA)-associated immune mediated organ specific diseases. Susceptibility is determined by environmental and genetic factors. Genetic factors are polygenic. It has been proven that concordance in monozygotic twins is 30-50% chance to develop the disease[5]. This indicates that many environmental factors still not identified are important in the development of type 1-diabetes[7]. HLA system is important in diabetes because it has been shown that majority (90%) of patients with DM 1 carry the HLA-DR3 and/ or DR4, while it is 35% in the normal population. Even stronger association is reported to be HLA-DQ region[5, 7].DM-1 is a autoimmune disease and is associated with other autoimmune disorders like thyroid diseases and Addison disease[5] .

Autopsies and biopsies of patients with diabetes type 1 have shown infiltration of the pancreatic islets beta-cells with mononuclear cells. This is known as insulinitis. Majority of

cells have been beta cell specific T-cells. Later also B-cells have been implicated an important role[5].

Auto-antibodies against pancreatic islet beta cells and other auto-antigen have been identified. They are present in 90% of new diagnosed patients. They were first known as islet cell antibodies (ICA) , they usually became undetectable after some years of disease. Today many islet cell antigens have been identified and some of them are insulin, glutamic acid decarboxylase (GAD) enzyme and the ICA[5-7].

Environmental factors are important in development of DM-1, but they are not well known. Exposure to enteroviruses such as coxsackie B4 has been suspected to be triggering factor, but no confirmation exist[5].

2.1.2. DIABETES TYPE 2 (DM-2)

Epidemiology

Prevalence of DM-2 is approximately 9 to 1 to DM-1 [1]. Type 2-diabetes is most prevalent in adult population, but incidence among adolescent is increasing, mainly among obese children and adolescents. Obesity has increased by 70% in age group 18-29 years, and diabetes type 2 has increased 70% in adult age 30-39 years over the last decade[8, 9]. This demographic trend has changed with increased prevalence of both obesity and type 2 diabetes in the young adults. Studies concerning the outcome of DM-2 versus DM-1 with early onset compared to the more common late onset type DM-2 has shown that early onset type 2 diabetes is more aggressive disease and leads to earlier cardiovascular complications[9].

Etiology

DM-2 is today considered a major cause of premature deaths, predominantly form cardiovascular complications[4]. Abnormal insulin secretion, and impaired peripheral action of insulin are typical features [10]. The cause of the disease is combination of genetic and environmental factors. This disease is observed in families and monozygotic twins of patient with type 2 diabetes has greater than 90% chance to develop diabetes[11]. Interestingly some populations like the Pima Indians had such a high prevalence of type 2 diabetes that it could only be explained by genetic causative factors[9]. Most types of DM-2 are polygenic, but MODY is a exception[6, 10]. It is linked to mutations in approximately 10 genes and is usually autosomal dominant inheritance. Correct diagnosis is important because its treatment can be different. MODY is characterized by high penetrance and severe impairment of insulin secretion[6, 12].

Environmental factors in development of DM-2 are many and obesity is the best known. This is a major problem especially in well fed populations like in USA and countries in Europe. Metabolic syndrome (syndrome-X) is associated with type 2 diabetes. It consist of central obesity, Hypertension, hyperglycaemia, dyslipidemias and is linked to insulin-resistance[10, 13].

2.2. PATHOPHYSIOLOGY OF DIABETES MELLITUS

DM-1 and DM-2 both have in common increased level of blood glucose. Insulin and glucagons are the two most important hormones for glucose homeostasis[1]. Other important regulating hormones are epinephrine, ACTH, growth hormone and glucocorticoids. They are occurring under many different circumstances i.e. stress. Insulin is released by the beta-cells of pancreas in response to increased blood glucose. It lowers blood glucose by suppressing glucose production and stimulates uptake of glucose by cells mainly in liver and skeletal muscle. In addition insulin suppresses lipogenesis in fatty tissue and it stimulates amino acid production in skeletal muscle. On contrary in fasting-state, insulin secretion is suppressed and glucagons secretions from pancreas alpha-cells increase. It is opposing the action of insulin and thereby increased glucose release and production (gluconeogenesis and glycogenolysis)[1].

DM-1 symptoms and signs appear when 90% of the islet cells are destroyed[1]. DM-2 early stage is characterised by reduced sensitivity to insulin and therefore compensatory hyper-insulin production[1]. The clinical signs and symptoms can appear when muscle and fat tissue sensitivity to insulin has decreased below 50%- 35% of normal[1]. The fact that symptoms and signs appear late or years after the disease start shows that the human body has great safety factor for glucose control[1]. It is therefore very important to diagnose and start preventive measures and treatment of the disease as early as possible. Because of easy diagnostics and good treatment options the disease can be controlled and life threatening complications like neuropathy, cardiovascular diseases and nephropathy can be delayed or avoided[1].

Pre-diabetes means a state of moderate impaired blood glucose control and high risk of complications. Most commonly the first complications to appear are retinopathy and cardiovascular diseases. Diagnostic criteria for pre-diabetes are when fasting blood glucose exceeds 5.6mmol/l and/ or 2 hour glucose in a glucose tolerance test exceeds 6.9 mmol/l[1].

DM-2 usually have a longer pre-diabetic phase than type 1, this is explained by compensatory hyperinsulinemia [1].

2.3. CLINICAL FEATURES.

The clinical presentation may be acute and subacute. Acute presentation is typical in young people and they classically present with polyuria, thirst and weight loss. Ketoacidosis may be the presenting symptoms in type 1 diabetes usually if not these early symptoms are discovered[14].

Subacute presentation is mostly in older patients and the clinical onset may be over months or years. Polyuria, thirst ,weight loss is typical, but also atypical presentation like fatigue, visual disturbances, infections of genitalia, pruritus vulvae and balanitis caused by candida infection are common[14].

2.4. COMPLICATIONS OF DIABETES

Acute diabetic complications

Hyperglycaemia may result from absolute or relative insulin deficiency. In some patients, the condition may culminate in diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar coma. Profound hypoglycaemia may result from a relative excess of insulin. Symptoms associated with acute hyperglycaemia generally develop more slowly (over hours or days) than do symptoms associated with an acute fall in the level of blood glucose (over minutes)[15].

Long term or chronic complications

They are often caused by microvascular or macrovascular complications. Microvascular disease is specific to diabetes and affects small vessels throughout the body. Most important are the three sites retina, renal glomerulus and nerve sheaths. These complications tend to occur 10-20 years after diagnosis in young patients, in older patients they appear sooner[8, 16]. Macrovascular complications are most common in western society. Diabetes is a risk factor for the development of atherosclerosis[8]. This leads to increase in prevalence of stroke and myocardial infarct among diabetics[4, 15, 16].

2.5. DIAGNOSIS OF DIABETES

Anamnesis (symptoms, signs, family history) Physical examination(Evidence of weight loss, dehydration, ketone foetor) or evidence of complications of diabetes like vision defects, neuropathy with decreased peripheral sensation or numbness.

Laboratory investigations with measurement of blood glucose, urine screening for glucose and protein, HbA1c, C-peptide, full blood count, renal function test, liver function test and Auto-antibodies testing in type 1 diabetes[4].

WHO criteria for diagnosis[17].

1. Fasting plasma glucose more than 7.0mmol/l.
2. Random plasma glucose more than 11.1mmol/l.
3. One abnormal laboratory value is enough in symptomatic patient, but in asymptomatic patient two abnormal values are needed.
4. The glucose tolerance test is important in establish the diagnosis. Impaired glucose tolerance is per definition blood glucose between 7.75-11.1 mmol/l. Diabetes criteria is values above 11.1 mmol/l. Fasting plasma glucose between 6.1 and 7.0 mmol/l is said to have impaired fasting glucose tolerance.(Clinically important because those with impaired glucose tolerance are at risk of developing type 2 diabetes and also to detect gestational diabetes[17]). Pre-diabetes is diagnosed when fasting blood glucose is more than 5.6 mmol/l or 2 hours glucose tolerance test is more than 6.9 mmol/l[1].

2.6. PREVENTION AND TREATMENT OF DIABETES

It is important with preventive measures to avoid development of diabetes. Primary prevention is consisting of education and promotion. Secondary prevention should focus on the early detection and treatment to stop development or control disease. Tertiary prevention mostly focuses on prevention of the complications of diabetes. It exist many barriers to the preventive measures and common is lack of information, lack of time in the consultations, bad compliance and more[18]. Prevention and treatment of diabetes is a multidisciplinary task. Many modalities exist, and important is education and lifestyle changes including diet, exercise, weight-reduction, decreased alcohol consumption and quit smoking. These are the key to successful prevention and treatment of type 2 diabetes. If primary preventive measures fail it is possible to use oral anti-diabetic drugs, or even insulin in type 2-diabetes. Pharmacologic treatment is the best way to treat type 1-diabetes. Preventive measures toward type 1-diabetes is today not known, but it is believed that T-cells will be the main target in future preventive measures[7]. Through the diabetes clinical control trial (DCCT), it was proven that intensive glycemic control, control of blood pressure and lipid control can delay complications of diabetes [4, 19]. This is most valid for type 1-diabetes and not type 2[16]. If the above mentioned modalities fail it is possible to treat diabetes with pancreas transplantation or islet cell transplantation[7].

The American diabetic association recommend treatment target HbA1c less than 7%, blood pressure less than 130/80mmhg, s-LDL less than 2.6mmol/l, TAG less than 1.7mmol/l and HDL more than 1.1mmol/l[4].

2.6.1. Lifestyle and education

1. Education: patients must be informed about the danger and possibility to treat their disease and haw they best can live with the disease. Education in self monitoring of blood glucose is important.

2. Diet: Many studies have shown the connection with overweight and certain diets to development of diabetes type 2. (ATTICA study) Good dietary habits can prevent and improve type 2-diabetes, obesity and delay or stop other complications[20].

3. Physical exercise: Used in combination with diet to reduce weight.

4. Alcohol binge consumption should be avoided, it can lead to severe hypoglycaemia in type 1 diabetics. Also alcohol has high energy content, therefore it should be used only moderately.

5. Smoking is associated with atherosclerosis, claudication and together with diabetes it worsens the perfusion of feet.

6. Weight reduction: Obesity is tightly connected with prevalence of type 2-diabetes and metabolic syndrome. Maybe the most important preventive measure to prevent and treat type 2-diabetes[21].

2.6.2. Pharmacologic treatment

1. Insulins: They are used mostly in type 1 diabetics and sometimes in type 2 diabetics. They are divided into very short acting, short acting, intermediate acting and long acting[16]. It exist more ways to administer insulin among them are insulin pens, insulin pumps and inhalation. Different treatment protocols exist, and ideally the administration should mimic the natural secretion of a normal pancreas.

2. Oral anti-diabetic drugs: Most used in type 2 diabetics. It exist more types of drugs and the main groups are sulphonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones and meglitinides[22].

3.Other drugs: Anti-obesity drugs(Orlistat)[22], Anti-hypertensiv drugs, cholesterol lowering drugs[4].

2.6.3. Other

Pancreas transplantation or islet cell transplantation[7].

3.0. DIABETIC NEUROPATHY (DN)

Neuropathy is a common complication of diabetes. It is defined as signs and symptoms of peripheral nerve dysfunction in a patient with diabetes mellitus, and other causes are excluded[2]. The vascular hypothesis with occlusion of the vasa nervorum is considered a main cause. All types of diabetes (DM-1, DM-2 and secondary diabetes) can lead to neuropathy. The incidence of neuropathy increases with duration of diabetes[2]. The prevalence of neuropathy in diabetes patients approaches 70%[1]. It has great variety of clinical presentations. But in general somatic and autonomic nerves are affected, it can be asymmetrical or symmetrical, distal to proximal or not, it can be dominant sensory nerves or motor nerves affected[1].

3.1. TYPES OF DIABETIC NEUROPATHY

There are three major types of diabetic neuropathy[23].

1. Distal symmetrical polyneuropathy.
2. Focal neuropathy.
3. Autonomic neuropathy.

In addition there are some other specific types of diabetic neuropathy like acute and chronic painful neuropathy and diabetic amyotrophy[2].(proximal asymmetric neuropathy)

3.1.1. DISTAL SYMMETRICAL POLYNEUROPATHY (DSP)

DSP is the most common of the diabetic neuropathies. It probably account for 75% of all diabetic neuropathies[2]. Typically it is bilateral manifested, distal to proximal direction and sensory symptoms dominate over motor symptoms. The onset and course of illness is different from patient to patient, but increasing age, male sex, increasing height, longer duration of diabetes, hypertension, poorer glucose control, alcohol consumption, and smoking may be independent risk factors[1, 2].

Early clinical signs are loss of pain sensation, vibration sense and temperature sense in the foot. Sensory symptoms can be divided into two broad categories, positive and negative symptoms. Positive symptoms include pain , paresthesias, and increased sensitivity to normal painless stimuli(allodynia and hyperalgesia) Negative symptoms consist of loss of sensory perception.(vibration, thermal, tactile, nociception.)[1] Small and large nerve-fibers are affected[2]. Motor symptoms are rarer than sensory, but they are negative and typical present with muscle weakness and later muscle atrophy[1].

3.1.2. FOCAL NEUROPATHY

Focal neuropathy is rare, and it is believed to be caused by acute occlusion of a blood vessel with the resultant ischemia in a nerve or group of nerves. It is typically of sudden onset, an asymmetrical nature, and a self-limited course. Near total recovery generally occurs within two weeks to 18 months. Examples of focal diabetic neuropathies are cranial neuropathies(Typically eye muscle innervation), truncal neuropathies, mononeuropathies, radiculopathies, and plexopathies[2]. Both sensory and motor components may be present[23].

Carpal tunnel syndrome is a typically complication of diabetes, but is more a result of entrapment than direct metabolic nerve damage[9].

3.1.3. DIABETIC AUTONOMIC NEUROPATHY (DAN)

Sympathetic and parasympathetic nervous system and various organs of the body may be affected. Organ systems mostly affected is cardiovascular system(orthostatic hypotension and painless myocardial ischemia), gastrointestinal tract(gastroparesis, constipation, diarrhea, and fecal incontinence), genitourinary system with bladder dysfunction and impotence, abnormal papillary function, sudomotor neuropathy (sweating)and vasomotor function[2, 23]. Its presentation may be various and often it may be unnoticed for long time. It is among the least understood diabetic complication, even though its impact on human survival and quality of life is tremendous[24].

DAN may appear as early as one year after diagnosing diabetes. It frequently coexisting with other peripheral neuropathies and its severity often correlates with the severity of somatic neuropathy[2, 24].

3.2. PATHOGENESIS OF DIABETIC NEUROPATHY (DN)

Multiple etiologies and hypothesis includes causes like metabolic (hyperglycaemia)[9], neurovascular insufficiency, autoimmune factors, neuro-hormonal growth factor deficiency insulin signalling defects and cellular mechanisms[1]. Despite long lasting efforts have been done to learn more about the pathogenesis, it remains poorly understood.

3.2.1. HYPERGLYCAEMIC HYPOTHESIS

DN follows both type 1 and 2 diabetes, and both have hyperglycaemia in common therefore the hypothesis about hyperglycaemia as cause for DN was launched. Many proofs have shown that better glucose control in diabetes patients decreases or delays the development of DN[16]. Pathophysiologically it is explained by activation of the polyol metabolic pathway

through the enzyme aldose reductase leading to accumulation of sorbitol and fructose and potential changes in NAD:NADH –ratio. This induces non enzymatic glycosylation of structural nerve fiber-proteins[1, 2]. Other mechanisms are that hyperglycaemia induces oxidative stress with increased free radical production which leads to vascular endothelium damage and reduced nitric oxide available. Activation of Protein kinase C (PKC) via glycolysis has been linked to vasoconstriction and decreased neuronal blood flow. All these changes in glucose metabolism leads to abnormal neuronal, axonal and schwann cells metabolism with the result of decreased axonal transport[2]. There are some difficulties with the hyperglycaemic hypothesis. Many studies on animals and humans have showed that hyperglycaemia may be an important factor for triggering of DN, but after correction of blood-glucose level in animal studies the progression of the disease continued anyway. This example and many more has lead to the belief that it has to exist some other factors for maintaining DN, and/or maybe trigger it[1].

3.2.2. VASCULAR HYPOTHESIS

Among many possible causes of DN, this is one of the best known. It is believed to be because of occlusion of vasa nervorum as the prime cause. Vasa nervorum is the main feeding blood vessels to the nerves. Microvascular damage to vasa nervorum is a common microvascular complication of diabetes[1, 16]. Atherosclerosis, glycosylation end products, free radicals, activated PKC and immune mechanisms may contribute to vascular occlusion of vasa nervorum of the nerve sheath[1]. This leads to endoneural hypoxia that further leads to capillary damage. This can escalate to disturbed axonal transport and reduced Na-K- ATPase activity which leads to axonal atrophy and impaired axonal transport[24].

3.2.3. OTHER POSSIBLE FACTORS FOR DEVELOPMENT OF DIABETIC NEUROPATHY

Insulin and insulin receptors may also play an isolated role in development and maintenance of DN. Insulin receptors are mainly found in liver, skeletal muscle and in fatty tissue. But are also expressed in high density in endothelial cells, schwann cells and sensory neurons[1, 2]. Because of this localisation of the insulin receptors it is thought that correction of insulin levels in DM-1 and insulin sensitizing therapy in DM-2 not only correct glucose levels but also secure its independent effect on peripheral nervous system (PNS)[1].

Impairment of intracellular insulin signalling in PNS is another suggested hypothesis as cause for peripheral neuropathy. This applies to both DM-1 and DM-2. It is especially applicable to pre-diabetes, and diabetic neuropathy development[24].

Other suggested possible causes are the role of insulin like growth factor (IGF) and C-peptide[24].

3.3. DIAGNOSIS OF DIABETIC NEUROPATHY

Qualitative and quantitative diagnostic methods can be used. Anamnesis(including family history, specific symptoms like pain, paresthesias, numbness, weakness, symptoms of hypoglycaemia, orthostatic light-headedness, symptoms from GIT like bloating, nausea, vomiting, constipation, diarrhea, incontinence of stool. Uro-genital symptoms of loss of bladder function, sexual dysfunction, repeating urinary tract infections[2]

Physical examination including assessment of muscle power, pinprick sensation distally on all limbs, distal thermal sensation, joint position sense, sense of vibration and ankle reflex(may be decreased normally in old above 70 years[2, 23].

Clinical testing of autonomous nervous system function can be done by more ways. In the early 1970`s Ewing et.al. suggested five simple non-invasive cardiovascular reflex tests. (Valsalva maneuver, heart rate response to deep breathing, heart rate and blood pressure response to standing up and blood pressure responds to sustained handgrip.)[23, 24]

Specific tests are used to evaluate gastrointestinal, genitourinary, sudomotor function and peripheral skin blood flow[2, 24].

Nerve biopsy can exclude other causes of neuropathy. Skin biopsy has been used to quantify protein gene product 9.5, which is a panaxonal marker[23]. Nerve-conduction-studies is an important quantitative method used in documentation and follow up of patients with diabetic neuropathy. Both sensory and motor nerves can be measured[23].

3.4. TREATMENT AND PREVENTION OF DIABETIC NEUROPATHY

The main aim in treatment of DN is to prevent progression and to provide symptomatic relief[2]. The importance of prevention of complications from DN makes it important to detect and control diabetes and coexisting risk factors for neuropathy.(Smoking, alcohol abuse, hypertension.) this can prevent, slow down or delay the progression of DN.

The diabetes control complications trial (DCCT) demonstrated that diabetic patients that underwent tight glycaemia control reduced their risk of developing clinical neuropathy with 60%[16, 23] It set some standards concerning mean blood glucose levels and HbA1c levels in

follow up of treatment of DM patients. The American Diabetic Association (ADA) recommends HbA1c levels under 6.5% in both type 1 and 2 diabetics[23].

3.4.1. TREATMENT MODALITIES

When it comes to treatment and prevention of DN, other risk factors must be treated as well. This can be done by lifestyle changes (stop smoking, exercise, diet, reduce alcohol intake), pharmacological (anti-hypertensives, Statins or other cholesterol lowering drugs)[2]. Patients with *distal sensory neuropathy* are prone to develop foot/leg ulcer. They have lost or have decreased sensation and therefore lost protective reflex to injury. Inform patients with distal sensory or motor abnormalities about importance of foot care and wearing of special protective footwear and to avoid activities (such as jogging) that can traumatize the feet[23]. Pharmacologic therapy of DN is an alternative, many drugs have been tried[2]. Some examples are:

1.Aldose reductase inhibitors (ARI):Have been used for over 20 years in humans, but its efficacy has not been proved. Mechanism of action is to reduce flux of glucose to the polyol pathways.

2.Alfa- lipoic acid: a cofactor for dehydrogenase complex. It has been shown to reduce both somatic and autonomic diabetic neuropathy. In addition it is lipid lowering.

3.Carnitine: Acetyl L carnitine (ALC) Placebo controlled trial showed its effect on increased vibration sensation, decrease pain. Adverse effects were reported like pain , hyperesthesia, cardiovascular and gastrointestinal symptoms.

4.Neurotropic treatment: Recombinant Human Nerve Growth Factor was tried in two large trials, but was not found to be beneficial.

Symptomatic treatment is another important aspect of DN- management[2]. Painful neuropathies are common in diabetics and it affects life quality and morbidity in a negative manner. Examples of drugs used are tricyclic antidepressives (TCA), anticonvulsants(phenytoin, carbamazepine and gabapentin) selective serotonin receptor antagonists (SSRI), tramadol, capsaicin[2].

The pain caused by DN can be divided according to its character which reflects the type of pain-fibre affected. Pain is either Type C-Fibre mediated(unmyelinated sympathetic autonomic fibres)or type A-delta- fibre- mediated[24].
Typically Type-C pain is lacerating, burning and dysesthetic. Neurotransmitter is substance P. It can be treated by capsaicin and clonidine (sympathetic blocking action) or mexilletine.
Type A-delta fibre pain is deep, dull, gnawing pain that dony respond to the above mentioned drugs. Can be treated with antidepressants (TCA, SSRI), anti-convulsive drugs, tramadol.
Analgesics usually don't help, but studies has shown that Ibuprofen 400mg times 4/day relieve neuropathic pain. Narcotics should in general be avoided[2]. Other modalities consist of transcutaneous nerve stimulation, magnetic field therapy, infrared light therapy and spinal cord stimulation[2].

Focal neuropathy. After other causes are excluded, management is palliative. Spontaneous resolution generally occurs within a period of months but may persist over years[23].

Autonomic symptoms requires special attention in diabetic patients. Its management depends on the clinical presentation. Most dangerous is affection of the cardiovascular system with symptoms of orthostatic/postural hypotension. It can be treated with easy measures like raising the head-end of the bed when sleep, increase salt intake, small frequent meals and elastic stockings. Pharmacological treatment with drugs like beta-blockers can restore the parasympathetic-sympathetic balance[2].

4.0. LOWER URINARY TRACT DYSFUNCTION (LUTD)

Lower urinary tract includes bladder, urethra and the two urethral sphincters. Traditionally the problems were divided into abnormalities of emptying and storing of urine[25]. Treatment was directed towards the organ responsible for dysfunction. Modern approach is more holistic and takes under consideration the physiological, pathological overlapping systems in the pelvic region[25]. The major patient groups are those with bladder outflow obstruction, neurogenic disorders and incontinence for any reasons. Bladder outflow obstruction (BOO) can be primary or secondary. Primary BOO is a condition where the bladder neck fails to open adequately during voiding[25, 26]. Secondary BOO is for example because of benign prostatic hyperplasia (BPH). Hypothesis of etiology of primary BOO are fibrous changes of proximal urethra, muscular changes in trigone and/or external urethral sphincter and neurogenic causes[26]. Incontinence means involuntary urine leakage and mostly is seen as a

symptom secondary to dysfunction of urinary tract[26]. Incontinence is classified into more types (Urge, stress, owerflow and mixed)[27, 28]. Male and female LUTD may have different etiology and mechanisms because of anatomical and physiological difference of lower urinary tract and pelvis[29]. Neurogenic disorders are described more in detail below.

4.1. NEUROPHYSIOLOGY OF THE BLADDER.

The function of the urinary bladder is to store and empty urine. Voiding is a process where brain and spinal cord coordinate the activity of smooth muscle in bladder and urethra[30]. The lower urinary tract is innervated by three sets of peripheral nerves. They are lumbar sympathetic nerves (relax detrusor muscle and contract internal sphincter), sacral para-sympathetic nerves (contracts detrusor muscle and relax internal sphincter) and the third is pelvic pudendal nerve (control the external sphincter of bladder)[24, 30]. Afferent pathways (pelvic, hypogastric and pudendal nerve) send information to CNS about bladder filling and contractions which is of great importance for storage function and it also has a reflex action during micturation, which reinforce bladder contraction[30]. Afferent nerves are either C-fibers or A-delta –fibers. In general C-fibers mediate stretch response because of increase in volume. They also mediate nociception in response to overdistension of bladder wall. A-delta –fibers mediates sensation of fullness (tension of bladder wall)[30].

The communication between peripheral nerves and smooth muscle cells of the bladder is done by neurotransmitters and its receptors. Physiologically Acetylcholine binds cholinergic-muscarinic receptors in bladder muscle cells and is responsible for contraction. Muscarinic receptors have more subtypes, but in human 5 main types are identified, they are called M 1-5. M1,2,3 are identified by receptor binding assays in human bladder[30]. Most abundant is M2 and when acetylcholine bind to it, contraction is inhibited. Binding to M3 receptor in smooth muscle cells phosphoinositol is hydrolysed and intracellular calcium leads to muscle contraction[30]. Other system of parasympathetic control is the purinergic system. This system is not proved to exist in man, but many animal, pharmacologic and molecular studies showed its receptor and its influence on bladder contraction[30].

Alfa-adrenergic receptors and its neurotransmitters (noradrenaline) are under normal conditions not so important for bladder control, but under pathologic conditions its receptor density increases and stimulated it causes bladder contraction. Normally it has sympathetic effect with bladder relaxation[30]. Beta- adrenergic receptors in bladder are beta-1 and 2, but lately also beta-3 receptors is thought to be important in mediating bladder relaxation[30]. Nitric oxide (NO) is also thought to have effect on bladder control[30]. Intravesical

application of NO has showed to decrease contractility. Some other transmitters and receptors are of importance, like the tachykinins, Vanilloids and some others[30].

4.2. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION (NLUTD)

Etiology and epidemiology

NLUTD can be caused by damage of upper motor neurons (UMN) or lower motor neuron (LMN) by a many different diseases or injuries. Common causes to peripheral neuropathy are: Diabetes mellitus and alcohol abuse. Less prevalent causes are porphyriasis, sarcoidosis, guillain barre syndrome, some heavy metal intoxications and lumbosacral and genital herpes. In addition cauda equinae syndrome, disc disease, vaginal birth and iatrogenic causes are important[31]. CNS causes to NLUTD includes dementia, stroke, spinal cord trauma, tumors, basal ganglia disorders (Parkinsons disease, Huntingtons disease), infection of brain or spinal cord, multiple sclerosis and congenital myelomeningocele)[31].

4.3. CLASSIFICATION OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION (NLUTD)

The purpose of classification of NLUTD is to create better understanding, better communication between physicians and easier management of LUTD. Classifications are based on location of neurologic damage, neurologic lesion and LUTD, type of LUTD and functional classification[31]. The European Association of Urology (EAU), recommend use of the *madersbacher* clinical classification system[31]. This system is based on the bladder filling phase (over, normo or underactive detrusor) and voiding phase (Relaxation or non relaxation or detrusor sphincter dyssynergia (DSD)). A example is non relaxed sphincter or DSD in voiding phase will lead to increased or abnormal high detrusor pressure.(See Figure1)

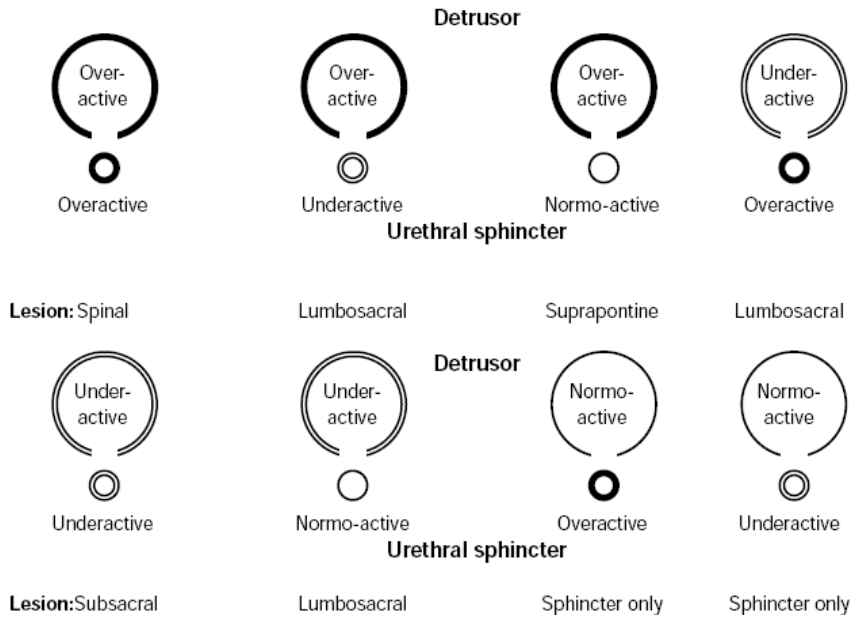

Figure 1. Madersbacher classification system with typical neurogenic lesions [31].

4.4. LOWER URINARY TRACT SYMPTOMS (LUTS)

LUTS can be divided into seven groups according to the international continence society (ICS) from 2001[25, 28]. Before this LUTS were classified according to pathology. But the modern understanding of lower urinary tract and its close relation to genital system has showed that overlapping between symptoms and pathology occur[25].

1. Storage symptoms: Increased daytime frequency (Pollakisuria), nocturia(urination during night), urgency, incontinence [25] (stress, urge, overflow and mixed) and enuresis(any involuntary loss of urine)[28].

a.Stress incontinence means involuntary leakage of urine during exertion, sneezing or on coughing. It is thought to be caused by weakness of external sphincter.

b.Urge incontinence can occur mainly in sensory or motor form. Sensory form means sensation of urge at low bladder volume because of early sensation without bladder contraction. Motor-form is associated with involuntary contractions at small volumes.

c.*Mixed type* is most common and consist of mix of urge and stress incontinence.

d.Continuous urinary incontinence is the state of continuous urinary leakage.

e.Other types are overflow incontinence typically occur when bladder pressure exceeds urethral pressure for example in overfilled bladder. Situational which can be associated with sexual intercourseor giggle incontinence.

2.Voiding symptoms: Weak stream, intermittency, splitting/spraying of urine stream, hesitancy, straining and terminal dribbling.

3.Postmicturition symptoms: Feeling of incomplete emptying, postvoidal dribble.

4. Symptoms associated with sexual dysfunction: Examples are dyspareunia, vaginal dryness and incontinence.

5. Symptoms associated with pelvic organ prolapse: Characterized by a low backache, heaviness and the need to digitally replace the prolapse to be able to void.

6. Lower urinary tract pain: Typically involves pain in bladder, urethra, vulva, vagina, scrotal, perineum and pelvis.

7. LUTD syndromes: For example genito-urinary pain syndromes. **[25]**

4.5. DIAGNOSIS OF LUTD

History: Ask about congenital and neurological diseases, previous pelvic surgery, urinary tract infections, number of pregnancies, child births, sexual function, bowel function, medications and allergies. Family-history concerning metabolic disorders and neurologic disorders. Specific history should elucidate detailed information regarding symptoms and signs of urine voiding or storage function like: frequency, urgency, nocturia, sensation of fullness, straining, incontinence, erectile dysfunction, paralysis, paresthesias, use of catheter, number of voidings per day. Sexual history and bowel history should be elucidated because of it might be affected by neurological dysfunction as well[31].

Physical examination: Attention to patient physical and mental status. Especially important with palpation of prostate in males and inspection if any pelvic organ descensus in woman. Neuro-urologic examination must be performed. Assessment of sensory, motor functions and reflexes of lower extremity, perineum and rectal areas. Check anal sphincter tone and bulbocavernosal reflex[31].

Other diagnostic methods: Biochemical and microbiological examinations of blood and urine (non-specific and specific tests), Imaging studies (Ultrasound, X-ray, CT, MRI…)

Urodynamic studies: Non-invasive tests like bladder diary and uroflowmetry and measure of residual urine can be used as first line and gives some impression of the patients lower urinary tract function. More reliable are the invasive urodynamic tests[26, 32]. Rectal ampulla should be empty and drugs that can affect lower urinary tract (LUT) should not be taken within 48 hours before the test. Different types of urodynamic study may be used. Filling cystometry can be combined with bladder pressure measurement and/or video urodynamics. [26, 32] and can objectively assess status of lower urinary tract in the filling phase, abnormal detrusor activity, low detrusor compliance and abnormal sensation of urge at low volume. Pressure flow study reflects the coordination of urthra, detrusor, and pelvic floor in voiding phase and may detect detrusor under activity, DSD, non-relaxing urethra and residual urine. Other measurement are urethral pressure measurement and video urodynamics [30-32]. In general these pressure –flow studies can identify three different clinical NLUTD. They are 1. Low detrusor pressure and high flow rate (Unobstructed), 2. High detrusor pressure and low flow rate (Obstruction) and 3. Low detrusor pressure with low flow (Poor detrusor contractility)[32]

4.6. TREATMENT OF NEUROGENIC LUTD

Non-invasive and invasive methods are used in LUTD caused by neuropathy or other pathology[25].

Non-invasive treatment:

Consist of increase of abdominal pressure by valsalva-maneovre or external suprapubic pressure(Credes maneovre.), lower urinary tract rehabilitation with for example pelvic floor exercise (Kegel), behavioral modifications (Bladder training), pelvic floor electro-stimulation and biofeedback[31].

Pharmacologic treatment:

Detrusor overactivity:

1.Anticholinergics(Tolterodine, trospium chloride, solifenacin, darifenacin and atropine) is used for hyperactive bladder[25, 30].

2.Mixed action drugs (Oxybutynin, propiverine).

3.Antidepressants (Imipramine), may be used in children with enuresis

4.Alpha-blockers (Alfuzosin, doxazosin, prazosin), decrease resistance in bladder outlet obstruction (BOO) [27, 32]

5.Beta-blockers (Terbutalin and salbutamol).

6.COX- inhibitors (Indomethacin).

7. Other drugs like baklofen, capsaicin, estrogen, desmopressin and botulinum toxin may be used[33].

Detrusor underactivity:

1. Oral bethanechol has shown some success in NLUTD patients. Except from this there are few pharmacologic alternatives[31].

Minimal invasive treatments: Catheterization, intravesical drug administration and electrostimulation. Bladder neck and urethral resistance can be decreased by chemical denervation of the sphincter. Botulinum sphincter injection can cure DSD. Sphincterotomy with staged approach, bladder neck incision and urethral stents can decrease outlet resistance as well[31].

Surgical treatment: Is often indicated in NLUTD if any of the above mentioned methods failed. Surgical procedures like urethral and bladder neck procedures (Sling, reconstruction of sphincter), bladder augmentation(replace or expand the bladder with intestine reduces the pressure effect of detrusor overactivity), bladder diversion (For example formation of a ileal catheterization reservoir), detrusor myectomy (enlarge bladder by removal of lateral detrusor

tissue to free entrapped ureter in a non-functional fibrotic detrusor)and denervation (sacral rhizotomy)[31, 32].

5.0. DIABETES MELLITUS AND LUTD

Urologic complications of diabetes include bladder dysfunction, urinary tract infection and sexual and erectile dysfunctions[29]. In this essay only the bladder dysfunction will be further described.

5.1. BLADDER DYSFUNCTION IN DIABETES PATIENTS

This is a common complication to diabetes along with other previously mentioned[34]. More than 50% of woman and men with diabetes have bladder dysfunction[29, 34]. Coexisting pathology that gives rise to bladder dysfunction must be considered, for example BPH in men and pelvic floor weakness in woman[29, 32]. Because of significant anatomical and clinical differences in man and woman concerning LUTD they are described separately[32]. Diabetic bladder dysfunction (DBD) is associated with many debilitating symptoms. The first urological deficit to appear in DBD is said to be loss of bladder sensation and with decreased bladder contraction it commonly lead to increased bladder capacity [35] , but interestingly some clinical studies in men and woman with DM have reported bladder instability and hypersensitivity as most frequent finding and decreased sensation as less frequent[29]. Typically it leads to a wide range of lower urinary tract symptoms like urgency, frequency, nocturia and incontinence.(Storage symptoms) and weak stream, hesitancy, incomplete emptying. (Voiding symptoms)[28, 29, 34, 36].

5.2. PATHOGENESIS

Bladder dysfunction caused by diabetes are thought to be a consequence of neuronal dysfunction (Diabetic neuropathy), bladder ischemia, alternation of smooth muscle cell function and structure in bladder wall, urothelial dysfunction, and possible other factors[29]. The most known mechanism is diabetic autonomic neuropathy[34], and already in 1864 diabetic neuropathy was referred to as a source of bladder dysfunction by Marshal de Calvi[35]. It is thought to cause damage to both afferent and efferent nerves[37], but the parasympathetic input system which is responsible for contraction is usually more affected than the sympathetic nerves which are responsible for bladder relaxation control[34, 36]. The earliest bladder autonomic dysfunction are sensory abnormalities, this has the consequence of elevated threshold for initiating the micturation reflex. This leads to asymptomatic increase in

bladder capacity and residual urine. Damage to efferent parasympathetic fibers commonly lead to decreased contraction and therefore voiding symptoms. If denervation continues of both internal and external sphincter it results in bladder overflow incontinence. Microvascular complications from DM may occur in bladder muscle and cause bladder dysfunction[36].

Diabetes may lead to hypertrophy of bladder wall due to mechanisms like organ adaptations to the increased urinary output because of osmotic diuresis and increased fluid intake. Bladder increase in weight and its urinary capacity is increased[34, 36, 37]. Studies performed on animals have showed many other connections between diabetes and bladder function changes[29]. Among them are alteration of receptors and ion-channels of bladder smooth muscles. Increase of muscarinic receptor density, Beta-1 receptor density, increased responsiveness to electrical stimulation of bladder strips in vitro and changes in calcium channel activity have been observed [29, 34, 37, 38]. In addition diabetes may affect the contractile proteins and its regulation, not too much study has been done on this, but some studies on induced diabetic rabbit has shown decreased smooth muscle contraction and increasing myosin light chain phosphorylation[36]. Other factors for neuronal dysfunction may be lack of axonal transport of nerve growth factor[30].

All in all these studies have given many controversies and still a lot is not known concerning the pathogenesis of diabetic bladder dysfunction[29].

Bladder urothelium has many functions in the bladder. Among them are barrier function for ions and urea and sensor for control of its function. In diabetes changes of its function and morphology may appear, but it hasn’t been extensively studied yet except that some studies of STZ induced diabetic rats where urothelium thickness was increased significant compared to its control[29].

5.3. BLADDER DYSFUNCTION IN MEN WITH DIABETES

Lower urinary tract symptoms (LUTS) in men are common. It is connected with age[39], hyperplasia of prostate, diabetes and other factors. Historically LUTS has been attributed to old men with hyperplasia of prostate, and this is true in most men more than 50 years. This classically gives the similar clinical picture on bladder dysfunction as diabetic bladder dysfunction (DBD)[29]. For this reason it was previously difficult to separate the two conditions, but today the diagnostic tools are better and the use of urodynamic study can objectively differentiate the two conditions[26, 32]. In addition some studies have shown that men with diabetes and BPH have more LUTS than men without diabetes, but how is not known[29].

Other studies have shown that BPH and diabetes affect different population of visceral afferents nerves supplying the bladder. In addition sodium and potassium channels are similar affected. These changes lead to changed excitability and detrusor overactivity, urinary frequency and with time impaired contractility due to myopathy[29]

The overlap in signs, symptoms and terminology that occur between BPH and LUTS from other reasons may be confusing[25, 29].

5.4. BLADDER DYSFUNCTION IN WOMAN WITH DIABETES

The most common bladder dysfunction in woman in general is urinary incontinence. In general approximately 50% of all middle aged and older woman has some form of incontinence[28]. It has a tremendous impact on life with limitations of daily activity, distress and decreased life quality[28]. Diabetes has among many other causes been identified as important independent risk factor. It is associated with a 30-100% increased risk according to studies, including the Nurses health study[29]. From this it was suggested that prevention of diabetes also will prevent DBD as urinary incontinence. Risk factors like obesity, positive family history and pregnancy all contribute to the development of LUTD and DM. DM-2 is associated with a 50-70% increased risk of incontinence[40]. The diabetes prevention program (DPP)[29] demonstrated that intensive lifestyle interventions involving weight loss and exercise reduced the incidence of diabetes in woman with impaired glucose tolerance (IGT) as well as the prevalence of urinary stress incontinence[28]. The conclusion of this study that contained 1957 overweight woman in high risk group for DM was that less frequent UI may be a powerful motivator for loosing weight[40]. Other common risk factors for DBD and especially UI are age[39] (2 peaks, one in the 5^{th} decade and second in the 8^{th} decade.), race (most studies done on caucassian woman, so little known about differences.), pregnancy, childbirth (Increase chance for UI, especially stress incontinence.), pelvic floor surgery, medications and menopause[28, 29, 32].

5.5. DIAGNOSING AND TREATMENT OF DIABETIC BLADDER DYSFUNCTION

Diagnosing of diabetic bladder dysfunction follows the same principles as in neurogenic lower urinary tract dysfunction. Anamnesis, physical examination, laboratory examinations, imaging methods and urodynamic studies. The most common early urologic deficit is loss of bladder sensation. This leads to a large capacity bladder that with cystometry shows a flat filling curve and little increase in pressure[35]. Typical symptoms of urinary retention then follows. Often a history of sexual dysfunction accompany the diabetic bladder

dysfunction[24]. Treatment generally follows the same principles as described previously for neurogenic LUTD[31].

6.0. DISCUSSION

Previously the current knowledge of LUTD and diabetes were described together with substantial evidence for the connection between diabetes mellitus and bladder dysfunction. Diabetic autonomic neuropathy is considered as main cause for diabetic bladder dysfunction[24, 29, 35]. Pathogenesis of diabetic neuropathy have many hypotheses and the glycemic hypothesis is supported by many scientists[1], but there are many issues that cant be explained by it[1]. Vascular causes are thought to contribute with damage to endothelium of microcirculation (vasa vasorum) to the peripheral nerves supplying the bladder [1, 24]. Hypertension and dyslipidemia often occur with DM-2 and metabolic syndrome which are risk factors for atherosclerosis which commonly lead to micro-vascular and macro-vascular complications[4, 9]. Patients with DM-1 and DM-2 that have been treated with tight blood-glucose control and treatment of additional risk factors like hypertension and dyslipidemia have reduced complication rates[16]. This shows the importance to diagnose and to treat coexisting pathology.

Animal studies made with induced diabetes on rats and rabbits have shown many specific connections between diabetes [29]. Knowledge of the polyol pathway in diabetic neuropathy lead to study with aldose reductase inhibitor in diabetic rats, and it is a good example of targeted specific treatment that may become important in the future [41]. Applied to humans is a complicated and long lasting process, but it gives hope that in the future even other and maybe better preventive measures and treatment of diabetic bladder dysfunction will be developed[25].

Diabetes mellitus can be isolated cause of bladder dysfunction, along with many other complications[2, 4]. Incidence of diabetes is increasing worldwide[4, 42] and as a consequence more LUTD will follow based on the fact that more than 50% of diabetics develops bladder dysfunction[29]. This fact obviously poses a real challenge, how to solve the problem? Main goal in management of diabetes and its complications are preventive measures and symptomatic relief[2]. Generally preventive measures can be primary, secondary and tertiary[18]. Primary prevention involves the completely asymptomatic individual with education and promotion to prevent disease[18]. DM-1 and DM-2 has different etiology and pathology[1] and therefore preventive measures may differ, but aim for all types of DM is to stabilize blood-glucose and prevent complications[2]. Education and promotion are the most important preventive measures in all types of diabetes[19]. DM-2 has a more clear preventive strategy than DM-1 due to its many proven environmental risk factors[4]. Obesity is one of most important risk factors for DM-2 and preventive and treatment strategies based on weight

reduction[21]. Primary preventive measures in DM-1 seems to be more difficult because of its strong genetic link and not known environmental factors[5, 16, 19]

Secondary prevention is identifying and treating asymptomatic persons who have already developed risk factors or pre-clinical disease[18]. Pre- diabetes phase is important because complications of diabetes starts to develop early[1]. Since prevalence of DM is increasing[3, 4, 42], more people are probably in a state of pre-diabetes, and therefore ideally they should be diagnosed early and preventive measures and treatment should be started[1, 4]. Pre-diabetes or impaired glucose tolerance may lead to severe impact on human health[4]. It has been linked to major problem of western lifestyle with obesity, lack of exercise as main contributing factors[7-9]. Tertiary prevention encompasses preventive measures in symptomatic patients where diabetic complications are clinically present[18] The main aim in prevention of LUTD caused by diabetes will be to stabilize blood glucose and other risk factors and to prevent further progression of bladder dysfunction[2, 4, 16, 29].

The fact that other pathological conditions like BPH, primary bladder outflow obstruction (BOO), prostatitis, stress urinary incontinence and Sexual dysfunction (impotence) may coexist with diabetes complicates the diagnosing and treatment of LUTD[25, 26, 43]. Since knowledge of pathogenesis in LUTD has been limited for long time it has resulted in rigid views on its treatment possibility, misunderstanding of the larger picture and confusing terminology[25], but as better knowledge and understanding of the complexity of LUTD developed, demands of better classifications and unison terminology came natural[25]. Symptoms can be divided according to international continence society (ICS) into 7 different classes[25, 28]. Diagnostic means are better and guidelines are made by international organisations like European association of urology (EAU)[31]. Traditionally pharmacologic treatment in LUTD was directed towards the muscarinic and adrenergic receptors on smooth muscle. Today it is clear that treatment has more targets like afferent neurons, efferent nerve terminals, urothelial cells and CNS[30]. All in all a more flexible view on LUTD than previously has been incorporated among urologists and maybe we are facing the truth of a complex understanding of the bigger picture? [25].

7.0. CONCLUSION

The existence of clear links between diabetes and lower urinary tract dysfunction has been known for longer time. Diabetic autonomic neuropathy is today still the main cause of bladder dysfunction, but it is generally agreement among scientists that diabetes causes LUTD by multiple mechanisms. Studies on animals have given both support and doubt to different hypotheses of diabetic bladder dysfunction. New views on pathogenesis of LUTD have lead to new challenges of diagnosis, treatment and preventive medicine. The classification and terminology of bladder dysfunction is today better than some years ago and this is important for doctors and patients. It makes the communication and diagnostic process easier, and therefore easier to choose correct treatment.

Preventive measures are the most important way to decrease the prevalence and incidence of diabetes and its complications. Primary prevention in form of education and promotion in form of lifestyle changes are of major importance to decrease the incidence of DM. Secondary prevention can be in form of early detection and good treatment of all types of diabetes. Tertiary prevention can be offered to those already suffering from the complication like LUTD (bladder dysfunction) associated with diabetes.

8.0. REFERENCES

1. Dobretsov, M., D. Romanovsky, and J.R. Stimers, *Early diabetic neuropathy: triggers and mechanisms.* World J Gastroenterol, 2007. **13**(2): p. 175-91.
2. Bansal, V., J. Kalita, and U.K. Misra, *Diabetic neuropathy.* Postgrad Med J, 2006. **82**(964): p. 95-100.
3. Mshelia, D.S., O.M. Akinosun, and F.M. Abbiyesuku, *Effect of increased patient-physician contact time and health education in achieving diabetes mellitus management objectives in a resource-poor environment.* Singapore Med J, 2007. **48**(1): p. 74-9.
4. Bryant, W., et al., *Diabetes guidelines: easier to preach than to practise?* Med J Aust, 2006. **185**(6): p. 305-9.
5. Tisch, R. and H. McDevitt, *Insulin-dependent diabetes mellitus.* Cell, 1996. **85**(3): p. 291-7.
6. Szepietowska, B., et al., *[Clinical, biochemical and immunological characteristic of diabetes type I, LADA, diabetes type II, and MODY patients]*. Pol Arch Med Wewn, 2002. **108**(6): p. 1177-84.
7. Gillespie, K.M., *Type 1 diabetes: pathogenesis and prevention.* Cmaj, 2006. **175**(2): p. 165-70.
8. Hillier, T.A. and K.L. Pedula, *Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth.* Diabetes Care, 2003. **26**(11): p. 2999-3005.
9. Eppens, M.C., et al., *Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes.* Diabetes Care, 2006. **29**(6): p. 1300-6.
10. Gerich, J.E., *The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity.* Endocr Rev, 1998. **19**(4): p. 491-503.
11. Malecki, M.T., *Type 2 diabetes mellitus and its complications: from the molecular biology to the clinical practice.* Rev Diabet Stud, 2004. **1**(1): p. 5-8.
12. Froguel, P. and G. Velho, *Molecular Genetics of Maturity-onset Diabetes of the Young.* Trends Endocrinol Metab, 1999. **10**(4): p. 142-146.
13. Chew, G.T., S.K. Gan, and G.F. Watts, *Revisiting the metabolic syndrome.* Med J Aust, 2006. **185**(8): p. 445-9.
14. Satterfield, D. and A. Lyons, *Development of a consensus publication by the Centers for Disease Control (CDC): the prevention and treatment of complications of diabetes--a guide for primary care practitioners,* in *Diabetes Educ*. 1992. p. 473, 475.
15. *Diabetes Control and Complications Trial (DCCT). Update. DCCT Research Group.* Diabetes Care, 1990. **13**(4): p. 427-33.
16. Havas, S. and T. Donner, *Tight control of type 1 diabetes: recommendations for patients.* Am Fam Physician, 2006. **74**(6): p. 971-8.
17. Mayfield, J., *Diagnosis and classification of diabetes mellitus: new criteria.* Am Fam Physician, 1998. **58**(6): p. 1355-62, 1369-70.
18. Dickey, L.L. and D.B. Kamerow, *Primary care physicians' use of office resources in the provision of preventive care.* Arch Fam Med, 1996. **5**(7): p. 399-404.
19. *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group.* N Engl J Med, 1993. **329**(14): p. 977-86.
20. Panagiotakos, D.B., et al., *The Relationship between Dietary Habits, Blood Glucose and Insulin Levels among People without Cardiovascular Disease and Type 2 Diabetes; The ATTICA Study.* Rev Diabet Stud, 2005. **2**(4): p. 208-15.
21. Charles, J., H. Britt, and S. Knox, *Patient perception of their weight, attempts to lose weight and their diabetes status.* Aust Fam Physician, 2006. **35**(11): p. 925-8.

22. Gillies, C.L., et al., *Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis.* Bmj, 2007. **334**(7588): p. 299.
23. Aring, A.M., D.E. Jones, and J.M. Falko, *Evaluation and prevention of diabetic neuropathy.* Am Fam Physician, 2005. **71**(11): p. 2123-8.
24. Vinik, A.I., et al., *Diabetic autonomic neuropathy.* Diabetes Care, 2003. **26**(5): p. 1553-79.
25. Heaton, J.P., *Lower urinary tract disease: what are we trying to treat and in whom?* Br J Pharmacol, 2006. **147 Suppl 2**: p. S2-13.
26. Nitti, V.W., *Primary bladder neck obstruction in men and women.* Rev Urol, 2005. **7 Suppl 8**: p. S12-7.
27. Imam, K.A., *The role of the primary care physician in the management of bladder dysfunction.* Rev Urol, 2004. **6 Suppl 1**: p. S38-44.
28. Al-Hayek, S. and P. Abrams, *Women's lower urinary tract function and dysfunction: definitions and epidemiology.* Minerva Ginecol, 2004. **56**(4): p. 311-25.
29. Brown, J.S., et al., *Urologic complications of diabetes.* Diabetes Care, 2005. **28**(1): p. 177-85.
30. Yoshimura, N. and M.B. Chancellor, *Neurophysiology of lower urinary tract function and dysfunction.* Rev Urol, 2003. **5 Suppl 8**: p. S3-S10.
31. Stohrer, M., et al., *The standardization of terminology in neurogenic lower urinary tract dysfunction: with suggestions for diagnostic procedures. International Continence Society Standardization Committee.* Neurourol Urodyn, 1999. **18**(2): p. 139-58.
32. Nitti, V.W., *Pressure flow urodynamic studies: the gold standard for diagnosing bladder outlet obstruction.* Rev Urol, 2005. **7 Suppl 6**: p. S14-21.
33. Andersson, K.E., *New pharmacologic targets for the treatment of the overactive bladder: an update.* Urology, 2004. **63**(3 Suppl 1): p. 32-41.
34. Liu, G. and F. Daneshgari, *Alterations in neurogenically mediated contractile responses of urinary bladder in rats with diabetes.* Am J Physiol Renal Physiol, 2005. **288**(6): p. F1220-6.
35. Buck, A.C., C.U. McRae, and G.D. Chisholm, *The diabetic bladder.* Proc R Soc Med, 1974. **67**(1): p. 81-3.
36. Su, X., et al., *Diabetes decreases rabbit bladder smooth muscle contraction while increasing levels of myosin light chain phosphorylation.* Am J Physiol Renal Physiol, 2004. **287**(4): p. F690-9.
37. Nakahara, T., et al., *MaxiK channel-triggered negative feedback system is preserved in the urinary bladder smooth muscle from streptozotocin-induced diabetic rats.* J Smooth Muscle Res, 2004. **40**(3): p. 97-109.
38. Tong, Y.C., W.T. Chin, and J.T. Cheng, *Role of sorbitol in the up-regulation of urinary bladder M(2) muscarinic receptors in streptozotocin-induced diabetic rats.* Neurourol Urodyn, 2002. **21**(2): p. 154-9.
39. Siroky, M.B., *The aging bladder.* Rev Urol, 2004. **6 Suppl 1**: p. S3-7.
40. Brown, J.S., et al., *Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program.* Diabetes Care, 2006. **29**(2): p. 385-90.
41. Kanda, M., et al., *Effects of ONO-2235, an aldose reductase inhibitor, on muscarinic receptors and contractile response of the urinary bladder in rats with streptozotocin-induced diabetes.* Jpn J Pharmacol, 1997. **73**(3): p. 221-8.

42. King, H., R.E. Aubert, and W.H. Herman, *Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections.* Diabetes Care, 1998. **21**(9): p. 1414-31.
43. Parsons, C.L., *Interstitial cystitis and lower urinary tract symptoms in males and females-the combined role of potassium and epithelial dysfunction.* Rev Urol, 2002. **4 Suppl 1**: p. S49-55.