

**STUDY ON FEATURES OF KNEE OSTEOARTHRITIS AND  
ASSESSMENT ON EFFECTIVENESS OF ORAL  
HYALURONIC ACID IN KNEE OSTEOARTHRITIS  
TREATMENT FOR THE ELDERLY WITH DIABETES**

**Scientific Instructor:**

**MD., PHD., ASSOCIATE PROF. PHẠM THẮNG**

**Director of Vietnamese Hospital for Gerontology**

**Hanoi University of Medicine**

**Hanoi-December 2011**

## INTRODUCTION

Diabetes mellitus (diabetes) is becoming a global issue and is considered as a pandemic of the 21st century. The disease ranks at the 4<sup>th</sup> -5<sup>th</sup> position on the cause of death in developed countries and is classified as non-contagious disease with the fastest growing rate. So far the world has about 246 million cases of diabetes, it is estimated that this number will double in 10 years. The explosion of diabetes, complications of the disease as well as associated diseases is the major challenge for the community [4]. In Vietnam, in 2001 for the first time, an epidemiological investigation of diabetes was conducted in accordance with international standards, the results showed that the rate of diabetes was 4.0%, IGT (Impaired Glucose Tolerance) was 5.1%, and the percentage of the risk factors was 38.5%. And especially, there are about 64.9% of people with diabetes are not examined and not treated properly [5]. At the same time a recent population survey showed that the elderly (> 60 years old) who constitute a significant percentage are also get diabetes with a high rate (> 10%). In addition, those elderly are also suffering from many diseases at once [4]. Therefore the problem of diabetes in the elderly should be more properly concerned. The factors may increase the risk of diabetes includes age, metabolic syndrome, physical inactivity, obesity and etc, and the diabetes often have other associated diseases, especially Osteoarthritis.

Osteoarthritis (OA) is a joint disease, characterized by disorders of the structure and function of one or more joints, the disease is common in all countries all over the world. In the United States, OA is a common disease affecting the more than 40% of the elderly and the annual cost for treatment is up to the billions of dollars [52]. In Vietnam, the epidemiological

investigation on diseases of musculoskeletal systems status in the community was conducted in 2002 in two residential areas: Trung Liet (Hanoi) and Tan Truong (Hai Duong) released that the OA disease accounted for the highest rate with 5.7% in rural areas and 4.1% in urban area [14]. The risk factors may increase the incidence of OA are age, obesity, metabolic syndrome and diabetes. OA risk in obese knee is higher up to 7 times than normal [34]. The OA treatment includes non-drug therapy and medications such as nonsteroidal anti-inflammatory drugs, analgesics, delayed effect anti OA drugs, in which Hyaluronic Acid (HA) is considered as the causal treatment for OA because it slows down the OA process.

Thus, the OA and diabetes type 2 will have the two same risky factors: age and weight. OA is not the cause of diabetes and vice versa; but people with diabetes who also have symptoms of pain in joints due to a sedentary lifestyle along with obesity will contribute much more difficulties to blood sugar (BS) control problems of the patients. Therefore, the ability of getting two diseases is very high and particularly in the elderly with obesity.

In Vietnam, so far there have not many studies on OA in the elderly diabetic patients as well as problems in the treatment among this group. Therefore, in order to ascertain this issue, we conducted a research: **“Study on characteristics of degradation of the knee joint and assessment on the effectiveness of oral hyaluronic acid in the treatment of knee joint degradation in with aged diabetes”**.

Target of the research:

***1. Describe the clinical and paraclinical characteristics of knee joint degradation in aged patients with diabetes.***

*2. Review the effectiveness of oral hyaluronic acid (Duo-Vital) and its safety in the treatment of knee joint degradation in aged patients with diabetes*

## **CHAPTER 1**

### **OVERVIEW**

#### **1.1. General introduction**

##### *1.1.1. History of diabetes:*

In 1500BC, the documents stored on paper by the ancient Egyptians described the symptoms associated with today diabetes typically frequent urination

In 1000 BC, Susruta one of the Hindu father of the Indian Medicine has noted signs of "Flies and ants swarm" in the urine of people with diabetes.

In 1st century AD, Diabetes (is siphon in Greece) was used to describe people with diabetes by Aretaeus (81-138 AD).

In 1674 AD, Thomas Willis was the first to compare the sweetness of sugar in the urine as honey, from which the term diabetets (a Latin word or Sweetened with honey in English) is widely used so far

##### *1.1.2. Definition of diabetes*

According to the World Health Organization (WHO): Diabetes mellitus is a syndrome characterized by hyperglycemia manifested as a result of the lack or complete loss of insulin or factors related to the decline in the secretion and activity of insulin.

According to the American Diabetes Association (ADA): Diabetes mellitus is a chronic disorder, with the following properties:

(1) Increase blood glucose.

(2) Combine with abnormal carbohydrate, lipids and proteins metabolism

(3) The disease is always associated with the development trend of kidney diseases, retinal, neurological, and other cardiovascular diseases.

### ***1.1.3. Diagnosis***

#### ***Standard of WHO in 2006:***

Diagnosis of diabetes has three criteria:

- Symptoms of diabetes (clinical): BS at any time is  $\geq 11.1$  mmol/l (200mg/dl); test 2 times.

- Fasting BS  $\geq 7.0$  mmol/L (126mg/dL); test 2 times.

- BS  $\geq 11.1$  mmol /L (200mg/dl) after 2h of making glucose tolerance test by drinking 75g of sugar (anhydrous) or 85g of sugar (monohydrate).

### ***1.1.4. Situation of diabetes disease***

#### **Situation of diabetes in the world**

At the end of the twentieth century and the early of twenty first century, diabetes has become one of the most 10 lethal diseases; the disease is increasing in developing countries, mostly Type 2, normally 9 out of 10 people with diabetes have Type 2. The explosion of diabetes Type 2 and the complications of the disease is a major challenge to the community. According to WHO, diabetes Type 2 accounts for 85-95% of people with diabetes [76].

According to a report by the International Diabetes Association:

- In 1994, the world has 110 million people with diabetes.
- In 1995, the world has 135 million people with diabetes accounting for 4% of the global population.
- In 2000 with 151 million people with diabetes.
- It is estimated that in 2025, there will be 300-330 million of people with diabetes, accounting for 5.4% of the global population. In which, the developing countries increase 42% and the developed countries increase by 17%. In Western Pacific Region, in 2005 there were 30 million people with diabetes and expected to be getting 50-60 million in 2050. Currently, the region has 12 countries with rate of diabetes above 8%, particularly in some island countries, this ratio may exceeds 20%. Also according to the WHO, in 2000, 10 countries with the highest number of diabetic patients all over the world include India, China, USA, Indonesia, Pakistan, Russia, Brazil, Italy and Bangladesh [76].
- In the U.S., according to the Centers For Diabetes Control and Prevention (CDC), diabetes increased 14% in 2 years, from 18.2 million people with diabetes in 2003 to 20.8 million years in 2005. Diabetes has become the leading cause of death in the US. Besides, the strongest increasing regions of the disease are now Asia and Africa. In Asia, in 1995, 62.5 million people were detected with diabetes, in which type 2 accounted for 61.5 million. It is expected that in 2010, 123.3 million people will have diabetes, in which type 2 is 120.1 million people [30].

### **Situation of diabetes in Vietnam**

In our country, under the investigation in 1990, a regional study that in some neighborhood of Hanoi, diabetes type 2 rates is about 1.2% and about 0.9% in Hue and 2.5% in Ho Chi Minh City. In 2001, an epidemiological investigation on diabetes and risk factors in four major cities (Hanoi, Hai Phong, Da Nang, Ho Chi Minh City) showed that the incidence of diabetes type 2 was 4.0%, the rates of IGT was 5.1%. The epidemiological investigation in 2002 also showed that the rate of diabetes Type 2 in the country was 2.7%, the percentage in the major cities was 4.4% [3].

The above statistics show that diabetes has increased alarmingly. However, even in developed countries like the US, over 50% of cases are not detected for years. Diabetes is considered as a costly disease in community. The cost for diabetic patients is 2-5 times higher than that for patients without the disease.

#### ***1.1.5. Characteristics of diabetes Type 2:***

- Heredity: Up to 60% - 100% of twins have diabetes Type 2. Children have diabetes then their parents are likely to get diabetes at 40% (or vice versa - ie adjacent generations); if the mother has diabetes, then the child will likely get higher than the case that the father has the disease. If both parents have diabetes, then the possibility of diabetes in their children is up to 70%.

- Obesity or overweight: Obesity is seen as a consequence of energy imbalance, over-capacity and result in lipid metabolism disorders. This is also a contributing factor in the process of increasing insulin resistance, which enable diabetes type 2 to develop. Obese men are at increasing risk for insulin resistance and reduction of the number of insulin receptors in cell membranes.

- Sedentary modes: inactivity mode is often associated with economic growth, urbanization growth, lifestyle changes, especially in developing countries.

- Age: the older the age is the higher the risk comes. This is one of risk factors which cannot be intervened.

- The special factors in history:

+ Infant who was born with weight less than 2500 g.

+ Women with a history of gestational diabetes or baby weighing over 4000g.

+ History of diagnosed IGT or fasting blood glucose.

+ Family history with a parent or child, brother, sister with diabetes.

+ Idiopathic hypertension.

+ Living environment changes.

### ***1.1.6. Treatment of aged diabetes***

- Diet and exercises mode: Many elderly with diabetes type 2 respond well to diet and exercises without medication. Gradual and modest weight loss is goals in treatment for patients with diabetes who are overweight or obese; diabetic patients will also need a regular exercises program suitable for motor ability and physical condition.

- Lower BS Drug:

+ Sulfonylurea: is the priority choice in patients without obesity. The treatment should start with low doses and gradually increase if the BS is not maintained at the permitted level. However, this can cause side effects of over lowering BS

+ Metformin: A choice for patients with overweight and obesity. Contraindicated when patients at risk of liver failure or kidney failure.

+ Alpha-glucosidase inhibitor: Can be used in combination with sulfonylurea or metformin group or alone. This drug has side effects on the gastrointestinal system; it is better to start with low doses and gradually increasing doses.

+ Repaglinid: The drug stimulates insulin secretion, it may be more appropriate for older than sulfonylurea for rapid effect and shorter duration, thereby reducing the risk of low BS.

+ Insulin: It is indicated when diet, exercise, and BS lowering drugs are not effective in controlling the BS or patients are suffering from associated acute diseases.

- However, the issue of treatment for the elderly patients with diabetes often faces many challenges because the diabetic elderly people often have several concomitant diseases and priority treatment is for each stage of the disease. The use of drugs can affect the BS such as the corticosteroids, estrogen, thiazid, phenytoin, glucosamine and so on also makes trouble to treatment for patients with diabetes.

## **1.2. General introduction on OA**

### ***1.2.1. Definition of OA***

OA (OA) is a common chronic disease in middle-aged and aged people; the disease is caused by cartilage damage as the result of biological processes and mechanical imbalance between synthesis and destruction of cartilage and bone under the cartilage. This imbalance can be started by several factors: genetics, development, trauma, metabolic [16].

## ***1.2.2. Classification of OA***

### ***1.2.2.1. Primary OA***

- Aging: As the main cause, appears later, usually in the next 60 years, hurt at many positions, slow progression and low severity.

- Heredity: The content of elements such as collagen and proteoglycan synthesis ability of cartilage is hereditary. Recently, it the diversity of collagen gene type 2 is discovered that the body of in a family disease of OA at an early stage [11].

- Endocrine factors and metabolism: menopause, diabetes, osteoporosis due to hormone.

### ***1.2.2.2. Secondary OA***

Mostly due to mechanical causes and the disease is caused by disorders which change the properties of cartilage and damage joint surface. The disease occurs in all ages (usually under 40), at several positions, severe and rapid in progression.

- History of trauma: bone or joint fractures, ligament rupture (shoulder joint ...), cartilage lesions, or after cutting semilunar cartilage, continual micro occupational injuries (hand joint, shoulder joint of the boxers; elbow joint of the workers operating the machine; basketball or weightlifting athlete's knee; Ballerinas' ankle; spine of the coal miners ...).

- The birth defects and developmental disorder: dysplasia and congenital dislocation of the hip, acetabular convex.

- History of surgery: Cutting semilunar cartilage

- History of bone diseases: Paget's disease or osteonecrosis.

- Bleeding disorders: 90% of patients with hemophilie have hem OA, usually in the knee, ankle and elbow. Relapsing hem OA causes synovial membrane proliferation, pushing the progression of secondary OA.

- Endocrine and metabolic disorders.

+ Acromegaly: over increase in hormone causes cartilage thickening then loss of elasticity and force bearing.

+ Cushing disease and usage of corticosteroids to inhibit function of immature bone cell formation can cause secondary hyperparathyroidism which stimulates the activity of osteoclasts and increase bone destruction process under the cartilage.

+ The crystal deposition in joint fluid: urate crystals (gout), Calciumpyrophosphat dehydrat (CPPD).

+ Ochronose or Alcaptonuria: a defective enzyme leads to accumulation of pigment which causes cartilage degradation in cartilage cells.

+ Chromosomal disease: There is iron deposition in articular cartilage and synovial membrane.

### ***1.2.3. Situation of study on OA***

#### ***1.2.3.1. Situation of study on OA in the world***

- All over the world there have been many authors studying the issues related to OA such as the causes and mechanisms of pathogenesis, clinical features and treatment.

Howell D.S [47] studied knee cartilage in the normal people and concluded that “Cartilage is developed and regenerated throughout life, the cartilage degradation process surpasses the synthesis time by time.

Bland J.H et al [35] have studied macro image and structure of articular cartilage of normal people and pathological changes of cartilage in OA patients. The results showed that cartilage has special structure consist of many fibers wrapped in basic substance. The fibers are collagen fibers, the surrounding basic substance is mostly proteoglycan substances associated with hyaluronic acid (HA). So when the HA is disrupted, and loses combination, OA process starts to occur.

Altman et al [33] also proposed the classification of OA as primary or secondary. The authors relied on finding or not finding the causes and risk factors from which they could build up the standard for diagnosis of knee and hip joint OA based on clinical symptoms and laboratory tests. The standard was later approved by ARA - American Rheumatism Association (1986) and applied until now

Lequesne [56] proposed diagnostic criteria for hip and knee OA based on radiographic and vulnerability classification of OA.

Dougados M et al [43] studied the role and effects of Diacerin (Artrodar) in the treatment of OA and concluded: Artrodar can reduce catabolism, increase the assimilation process, stimulate, increase intercellar components such as collagen, proteoglycan, HA in degenerative OA. This is a new trend in the treatment of OA.

Reginster JY et al [65] studied 319 patients with knee OA under treatment course: Oral Glucosamine Sulfate (Viartril ® - S) for 3 months at a dose of 1500 mg / day, 2 months without drugs to track and continue the treatment course as above for 3 years.

Rydell et al [62] was the first worldwide study of additional therapy with mucous (synovial) injection with HA in 204 patients with knee OA. With five

times of the injection, each time a week then 20-week of monitoring period, the results show clear signs of decreased pain, improved motor function in knee and it can achieve good levels from week 3.

Since then the therapies with mucus supply is widely used in Japan, Italy, [45], in Canada [31], in Europe [32]. Currently, hyaluronic acid has been put into therapy in OA of the knee among ARA - American Rheumatism Association and expand the treatment of OA in other joints such as ankle joint, shoulder joint, hip [37], [39].

### ***1.2.3.2. Situation of study on OA in Vietnam***

OA is a very common disease among diseases of musculoskeletal systems. OA rate is 4.66% of patients hospitalized at Bach Mai hospital (data 1991-2000).

According to epidemiological investigation on diseases of musculoskeletal systems status in the community in two residential areas: Trung Liet (Hanoi) and Tan Truong (Hai Duong) in 2002, OA patients accounted for the highest proportion: 5.7% in rural villages, 4.1% in the city [14].

- In terms of clinical characteristics and clinical studies there are followings:

Hong Hoa Dang [11] have studied the clinical characteristics and paraclinical of 42 patients with knee OA and found characteristics of knee OA in patients of our country as follow: 85.7% is female, 78,6% is at the age of over 50 and 64.3% is manual workers.

Thi Ai Nguyen [1] studied the clinical characteristics and application of standard for diagnosis for knee OA then concluded: knee OA diagnosed with ACR 1991 is in accordance with the conditions of Vietnam.

- Treatment:

In Vietnam, hyaluronic acid injection to joints in the treatment of knee OA has been applied since 2004. There have been studies on the effectiveness and tolerability of hyaluronic acid injection to joints in the treatment of knee OA. Hong Anh Thai conducted on 30 patients at the Nguyen Tri Phuong Hospital - Ho Chi Minh City, with 5 week course of injections, each injection a week then 12 weeks of monitoring, the author concluded: better effects of analgesic and function appear from the 3rd week.

Thu Ha Le et al [9] evaluated the effectiveness of Hyruan in the treatment of knee OA in 20 patients at the Central Military Hospital 108 also gives similar results.

Van Pho Nguyen et al [20] evaluated the effectiveness of HA on synovial injection in the treatment of knee OA and showed improvement especially in pain and expressions related to OA.

#### ***1.2.4. Diagnosis of OA:***

Based on clinical and subclinical characteristics

##### ***1.2.4.1. Clinical symptoms of OA***

- Location of lesions common in load-bearing joints.
- Subjective symptoms:
  - + Symptoms of pain at damaged joints: Usually mechanically
  - + Signs of joint stiffness and pain: Unlike morning stiffness, signs of joint stiffness and pain occur due to inactivity for a long period of time, usually occurring after a long nap or sitting for an extended period of time. However, these signs can reduce after a several movements

+ OA can cause a crackling noise (called "crepitus") when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons.

+ Reduced range of motion occurs when the joint becomes so deteriorated that it can't be fully contracted or extended, leaving the patient unable to fully extend their arms or legs. Arthritic fingers begin to curl in, and attempts to straighten them are painful.

- Objective symptoms:

+ Deformed joints develop as OA progresses. Bony spurs form at the site where bones are rubbing together. This usually occurs in the fingers, but can affect other joints (Heberden and Bouchat)

+ During evolution can be seen swollen joints hurt, or joint effusion, signs of wood shavings.

+ Occasionally, the joints may also be filled with fluid. Humid and cold weather increases the pain in many patients.

#### ***1.2.4.2. Paraclinical symptoms***

- Blood test: There is no inflammatory syndrome

- Synovial test: No Assembly inflammation, poor joint fluid cells

- Conventional X-ray test: typical X-ray image

+ Joint space narrowing: Cartilage separates the bones in joints; the area between the bones is the joint space. In conditions like OA, the joint space gets narrow because the cartilage wears away

+ Fibrosis under the cartilage, collapsed face under the cartilage

+ Pictures of the new bone formation: osteophytosis, bone spur

+ The cavity under the cartilage, sometimes the image of destroyed joints also appears

Standard radiographic diagnosis of OA by Kellgren and Lawrence [50]:

Stage 1: small bone spur or suspicious bone spur

Stage 2: obvious bone spur

Stage 3: Joint space narrowing at medium level

Stage 4: Joint space narrowing accompanied by fibrous bone under the cartilage

- Computer tomography, magnetic resonance image, adiaphanous in diagnosing lesions of neurological symptoms in patients with OA.

#### ***1.2.4.3. Standards for diagnosis of knee OA by the ACR 1991***

- Clinical, radiological, laboratory tests:

1. Knee pain.
2. Bone spurs at the edge of the bone joints (X-ray).
3. Joint fluid is degraded.
4. Age  $\geq$  40.
5. Stiffness less than 30 minutes.
6. Crunching when moving

The diagnosis is confirmed with the elements 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6.

- Simple clinical test:

1. Joint pain.
2. Crunching when moving

3. Stiffness less than 30 minutes.
4. Age  $\geq$  38.
5. Palpable enlargement of the bones.

Diagnosed with elements 1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5.

### ***1.2.5. Treatment of OA***

- The non-medication measures:

+ Weight loss.

+ Physiotherapy.

+ Reduce the load for damaged joints: Avoid work or position requiring overload

+ Exercises: Walking if the joints do not have lesions seen via X-ray image, swim or ride a bike.

- Treatment with medication:

+ Anti-inflammatory steroid.

+ Analgesic medication.

+Steroids drugs: Contra-indications when using for the whole body, only in where when needed.

- Anti-OA with delayed effects: Glucosamine, chondroitin, diacerein, hyaluronic acid.

+ Glucosamine sulfate:

Mechanism: Glucosamine sulfate is essential for the biosynthesis and stimulate cartilage cells to produce proteoglycan with normal structure.

Dosage: 1 to 1.5g/day.

Unexpected effects: Some patients with symptoms of gastrointestinal disorders. Some studies show that there is a rise in BS or unstable BS in diabetic patients with OA [61].

+ Diacerein (Artrodar): The drug is widely used in Vietnam and bring positive results.

Mechanism: as a molecule of anthraquinone group, it inhibits like 1 interleukin by reducing the quantity and sensitivity then protects the cartilage by monitoring the production of zytokine, stimulates cartilage cell to proliferate, stimulates cartilage cell to synthesis collagen type 2, proteoglycan and HA, which contributes to recover characteristics of synovial joint.

Oral dose of 100 mg/24h during at least 3 months

+ Unsaponifiable component of avocado and soybeans (Piaseledin).

Mechanism: it can work at the same time with interleukin 1, metalloptase, collagen, proteoglycan and cartilage cells, so it can reduce cartilage destruction.

The drug is widely used in Vietnam.

Dose: 0.3 mg/day, maintained for at least 2 months.

+ Chondroitine sulphate (Structun, Chondrosulf).

Mechanism: Inhibition enzymes causing cartilage loss, especially metalloproteasea enzyme.

Dose: 1g per day

+ Hyaluronic acid (Go-on, Hyalgan, Ostenil, Hyruan, OrthtoVise, Synvise) injections to joints.

- Endoscopy to clean joints and bones spurs.

- Surgery to repair the joint deformity, or artificial joint replacement.
- Implantation of cartilage cells or cartilage transplant.
- + Hyaluronic Acid (Go-on, Hyalgan, Ostenil, Hyruan, OrthtoVise, Synvise) đường tiêm nội khớp.

### **1.3. Hyaluronic Acid.**

#### ***1.3.1. Sketchy information of HA:***

- Since the 1970s, HA is described as a kind of mucilage, is a carbohydrate polymer molecules [33]. HA is an important component of joint fluid, which lubricates the cartilage, and it is a hydrophilic molecule and affects the elasticity of the cartilage.

- Components: HA in synovial fluid is a polymer composed of a polysaccharide chain connected continuously by pairs of glucuronic acid and N-acetylglucosamin synthesized in endothelial cells and released into synovial fluid. There is also HA in deep surface layer of cartilage cells[2], [57].

- Influential mechanism of HA in the treatment of OA: joint fluid has role of lubrication, reducing friction between the cartilage surface by movement and nutrition of joints. Joint fluid also helps to prevent the loss of proteoglycan by cartilage, indirectly enhancing HA inhibition or hyaluro by synovial membrane cells. In degenerative joint fluid, HA concentrations is lower than in normal joints (0.8 - 2 mg/lm compared to 2.5 to 3.5 mg / mL) and molecular weight of HA is also low (0.5 - 4 mega Dalton compared with 4-5 mega Dalton).

#### ***1.3.2. The development of mucous supplement therapy:***

- Mucus supplement therapy in the treatment of OA was conducted by Rydell et al [62] in the 1960s based on joint research of cattle, horses, and later on the human joints (normal OA and inflamed joints). The result of this study was as follows:

+ Elasticity of synovial fluid in normal people aged 20-25 is the highest, then age increases, the elasticity decreases. Reduced elasticity leads to reduced ability to protect articular cartilage surface.

+ In normal people, decrease of elasticity in synovial fluid is caused by three factors: Reducing interaction between HA molecules, reducing the average molecular weight of these molecules and concentration. All three of these factors often occur in case of inflammatory knee effusion.

- From 1968 to 1970 HA was put into the first clinical experiment in eye surgery and joint fluid supplement.

- End of 1970, the first clinical study on mucus supplement for the treatment of OA in human, was conducted in France by Rydell et al [62] it was performed on 200 patients with knee OA and 22 patients with hip OA and they also used saline injections as placebo. Effectiveness appeared after 1-2 s of HA then monitored 6-12 months; double blind study with a control showed clear analgesic effect (statistical meaning) and improved motor function significantly without side effects for the whole body, with very few side effects in place.

- Currently the use of HA by injection directly into joints is common in the health facilities with high technology and brought initial good results. Joint injections can only supplement HA to the injected joints while most of the cases reported were pain in multiple joints simultaneously. Furthermore, injections to joints only can be carried out by specialized medical staff of

Musculoskeletal Faculty and in sterile room with full of medical equipment, whereas risk of strokes and infection can occur

Nowadays thanks to the development of scientific technology, HA is manufactured in oral form. In this form, HA is used as a nutrient and directly absorbed through the gastrointestinal tract then released into the bloodstream and delivered throughout the body. Thus, the use of oral HA is convenient, easy to use and can be widely applied to joints than joint injection.

### ***1.3.3. Oral preparation of HA (Duo- Vital).***

- Ingredients: mixture of water and HA-Chondroitin Complex (HCC), sugar, vitamin E as DL-alpha-TocoPherolacerat, preservatives as Kaliumsorbitat (E 202).

- Working mechanism: HCC in Duo-Vital like other micro-nutrients is absorbed through the gastrointestinal tract into the circulatory system to activate the cell receptor CD44 in cartilage, which stimulate cartilage cells produce endogenous HA in order to increase HA in synovial fluid, HA and chondroitin supports each other in the protecting and providing nutrients to the cartilage. In this combination chondroitin can act better than a single type to cartilage.

- Usage: Drink after meals daily, 30ml/day for 30 days, may be repeated after 3-6 months.

## **1.4. Relation and pathogenesis of OA and diabetes**

### ***1.4.1. Relation of OA and diabetes***

The first evidence of strong association between OA and diabetes is the study dabiopsy histology of sternoclavicular joint on 200 subjects [68]. Another study with control group on 30 diabetic patients and 30 subjects in

the control group also showed significant changes on X-ray images, signs and symptoms of OA in patients with diabetes [72]. Studies have the same result that is the incidence of joint disease in general and OA in particular in diabetes groups is higher in the group without diabetes [69].

#### ***1.4.2. Basis of relation between OA and diabetes***

Since most cases of OA in patients with diabetes have renal manifestations, retinopathy, and vascular diseases, many authors suggest that OA progression is secondary to the neuropathy, vascular. Degenerative process is also related to the intermediate products of the chemical process of galactosamine and glucuronic acid of glycosaminoglycan chain, disorder in the process of mobilizing the sugar result in disorder in the formation of the polysaccharide chain then leading to the abnormal changes in the process of OA [58].

Increasing the chemical process of the collagen fibers due to prolonged hyperglycemia leads to obstructing collagen metabolism. Stiffness in patients with diabetes is due to abnormal collagen deposition around the joint, due to the chemical process of collagen fibers dependently or independently of enzyme with abnormal collagen metabolism [38]. Increase in blood insulin and insulin-like growth factors stimulates calcium at tendon heads which load the highest weight [42]

In contrast to other life-threatening complications for diabetic patients such as damage in micro and large blood vessels, the joint damage is considered as the multi-pathological factors or co-disease in patients with diabetes, so if detected early with timely intervention it can significantly improve quality of life of patients.

### **1.5. Issues in treatment of OA in diabetic patients**

- Exercises:

+ OA: Mode of exercise like walking is only applicable when there is no damage on X-ray, patients often have limited movement in the acute and severe phase

+ Diabetes Type 2: patients need to increase physical activity for the purpose of weight loss, especially in patients with overweight, obesity, thereby reducing insulin resistance. Training regime must suit their age, health status and personal preferences. Elderly patients with slightly increased BS just need to adjust diet and training regimen to bring about normal BS.

The implementation of the training regimen in elderly patients with diabetes type 2 and OA will face obstacles and contradictions, which make more difficult to control the BS.

- Drug therapy: Diabetes type 2 patients with OA have the treatment of pain killing anti-inflammatory and nonsteroidal and acetaminophen medication which can increase toxicity for the patients, moreover the use of glucosamine and chondroitin in prevention and treatment of OA also affects the BS of the patients. According to some studies, using high doses of glucosamine may increase the BS [65].

## CHAPTER 2

### SUBJECTS AND METHODOLOGY

#### 2.1. Subjects

##### *2.1.1. Standard for choosing patients:*

The patients over 50 diagnosed with diabetes were treated in the GNI from 3/2011 to 9/2011 (N = 270 patients).

##### **Standard for diagnosis of diabetes (WHO 2006) includes:**

- A sample of any blood with glucose  $\geq 200$  mg / dL ( $\geq 11.1$  mmol / L), test 2 times.
- Fasting glucose  $\geq 126$  mg / dL ( $\geq 7.0$  mmol / L) after at least 8 hours without eating, test 2 times.
- Blood sugar 2 hours after 75g glucose  $\geq 200$ mg/dl ( $\geq 11.1$  mmol / L).

Patients diagnosed with diabetes when there is any one of three above criteria.

The number of patients was calculated using the formula:

$$N = Z^2_{1-\alpha/2} * p(1-p) / (p * \epsilon)^2$$

In which:  $Z^2_{1-\alpha/2} = 1,96$  is Coefficient of reliability

$p = 0.325$  is rate of knee OA [17].

$\epsilon = 0.2$  is relative value

Apply the formula we have N = 200 (patients).

### ***2.1.2. Patients diagnosed with OA:***

- Patients with diabetes diagnosed according to WHO 2006 diagnostic criteria with following expression, will be diagnosed with OA:

+ Clinical: mechanical pain, no symptoms other places. It can be seen that the joint is deformed by bone buds.

+ Blood and / or joint fluid tests: Bilan-negative

+ X-ray: Joint space narrowing, especially the bones under the cartilage, the cartilage and bone buds, bone spur.

+ Diagnostic criteria of knee OA according to the ACR 1991.

Clinical, X-ray and laboratory:

- (1) Knee pain.
- (2) Spur at the edge of the bone joints.
- (3) Degenerative joint fluid
- (4) Age  $\geq 40$ .
- (5) Stiffness <30 minutes.
- (6) Bone crunching when moving

The diagnosis is confirmed with the elements 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6.

Simple clinical:

- (1) Joint pain.
- (2) Crunching when moving
- (3) Morning stiffness <30 minutes.
- (4) Age  $\geq 38$ .

(5) Palpable enlargement of the bones

The diagnosis is confirmed when the elements 1,2,3,4 or 1, 2, 5 or 1, 4, 5

**2.1.3. Standard for cross out the patient lists:**

- Patients do not agree to participate in research.
- Infections in OA and systemic infections.
- Standard for cross out the patients in accordance with the objective 2: signs of OA patients at stage III and IV according to Kellgren and Lawrence classification. There are diseases associated with: Liver failure, kidney failure, heart failure.

**2.1.4. Place and time:**

- Study location: National Geriatric Institute (NGI)
- Research duration: From 3/2011 to 9/2011.

**2.2. Methodology:**

**2.2.1. Methodology**

- Objective 1: cross-sectional and descriptive study
- Objective 2: prospective study with intervention.

We apply the method of conducting a medical examination to gather information about the epidemiological characteristics, the rate of OA, clinical and paraclinical symptoms of patients diagnosed with diabetes and treated in NGI from 3/2011- 9/2011, and evaluate the effectiveness of oral HA in treatment for patients with diabetes and OA.

- Oral HA supplement (DUO VITAL).

- Evaluation of clinical efficacy, blood sugar changes and undesirable effects on clinical practice.

### **2.2.2. Means of research:**

- Oral HA (DUO VITAL) with ingredients: mixture of water and HA-Chondroitin Complex (HCC), sugar, vitamin E as DL-alpha-Tocopherolacetat, preservatives as Kaliumsorbat (E 202).

- Usage: after meals daily, 30ml/day for 30 days

### **2.2.2. Stages**

#### **2.2.2.1. Data collecting**

Each patient was recorded with information in a medical record form (Appendix). To meet the aims of the research study, we deeply explore the following issues:

- Age, sex, literacy, diabetes duration
- The symptoms of OA.
- Subjective, constitutional and objective symptoms is detected and treated.

- Patients were measured with height (in meters, error not exceeding 0.5 cm), weight (in kg, the error does not exceed 100 g), waist, butt (in cm), patients is fatty abdominal with waist circumference  $\geq 90$  cm (men) or  $\geq 80$  cm (women).

- BMI - Body Mass Index

$BMI (kg / m) = weight (kg) / [height (m) * height (m)]^{-1}$ .

Classification of BMI according to the Southeast Asian Diabetes  
Association 2001

<b>BMI</b>	<b>Classification</b>
< 18.5	Thin
18.5- 22.9	Normal
23- 24.9	Overweigh
$\geq 25$	Obesity

- Measuring blood pressure: All patients were measured: Increased BP was defined as (systolic blood pressure) SBP  $\geq 140$ mmHg and / or diastolic high blood pressure  $\geq 90$ mmHg.

- The biochemical tests: Made in the department of biochemistry - Central Geriatric Institute.

1) Fasting SB.

2) SB after meals.

3) HbA1c: Tracking changes in HbA1c at the start of the study (T0) and after 3 months (T3).

4) Microalbuminuria

5) Bilan lipid: cholesterol, triglycerides, HDL-cholesterol, LDL-Cholesterol.

Dyslipidemia classification as recommended by the Vietnam Heart Association:

<b>Parameters</b>	<b>Normal</b>	<b>Imbalance</b>
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Cholesterol	< 5.2 mmol/l	≥ 5.2 mmol/l
Triglycerid	< 1.7 mmol/l	≥ 1.7 mmol/l
HDL- Cholesterol	> 1.0 mmol/l	≤ 1.0 mmol/l
LDL- Cholesterol	< 3.1 mmol/l	≥ 3.1 mmol/l

6) Renal function: urea, creatinine, proteinuria, hematuria microscopic.

- Blood formula: The normal white blood cell counts from 4-10 G/l, patients with inflammatory signs have WBC > 10G/l
- Erythrocyte sedimentation rate (ESR)
- ECG
- Radiographic of damaged joint: all patients with suspected knee OA will be taken to X-rays room of Central Geriatric Clinic for radiographic test.

Conventional radiography of damaged knee is taken in 2 positions (straight - inclined). Reviews on radiographic images: Joint space narrowing, especially the bones under the cartilage, bone spurs. Diagnosis of knee OA degree via X-ray images is according to Kellgren et al.

- MRI damaged joint if indicated.
- Using WOMAC (Western Ontario and McMaster Universities) to assess the degree of OA includes the following parameters:

+ WOMAC A: Review of pain signs appearing when doing the following activities:

(1) Walking.

- (2) Climbing the stairs.
- (3) Pain at night.
- (4) At rest (lying or sitting).
- (5) Standing (with strength of body weight).

+ WOMAC B: Review of stiffness.

- (1) Morning stiffness.
- (2) Stiff joints at the end of the day.

+ WOMAC C: Review of motor function.

- (1) Down the stairs
- (2) Up the stairs
- (3) Change in posture from sitting to standing.
- (4) Standing
- (5) Bending
- (6) Walking
- (7) Up or down cars.
- (8) Shopping.
- (9) Wearing socks.
- (10) Getting up out of bed.
- (11) Take of socks
- (12) In bed.
- (13) Sitting
- (14) Toileting (standing up or sitting down)

(15) Working (heavy work).

(16) Working (light work).

(17) Changing clothes when showering and toileting

Scale for the review is as follows:

Level	Scores
None	0
Low	1
Medium	2
Heavy	3
Very Heavy	4

Review:

Total WOMAC score:

- Minimum score: 0

- Maximum score: 96

WOMAC A: pain

- Minimum pain score: 0

- The maximum pain score: 20

WOMAC B: Stiff joints

- The minimum stiffness: 0

- The maximum stiffness: 8

WOMAC C: motor function

- The minimum motor function: 0
- The maximum motor function: 68

WOMAC rating scores at the start of the study (T0), after 1 month (T1), after 2 months (T2).

### **2.3. Data process:**

We use the data processing program SPSS 16.0. The data were calculated with 95% reliability (level of statistical significance  $\alpha=5\%$ ). Meaning of algorithms are identified by the method of biostatistics.

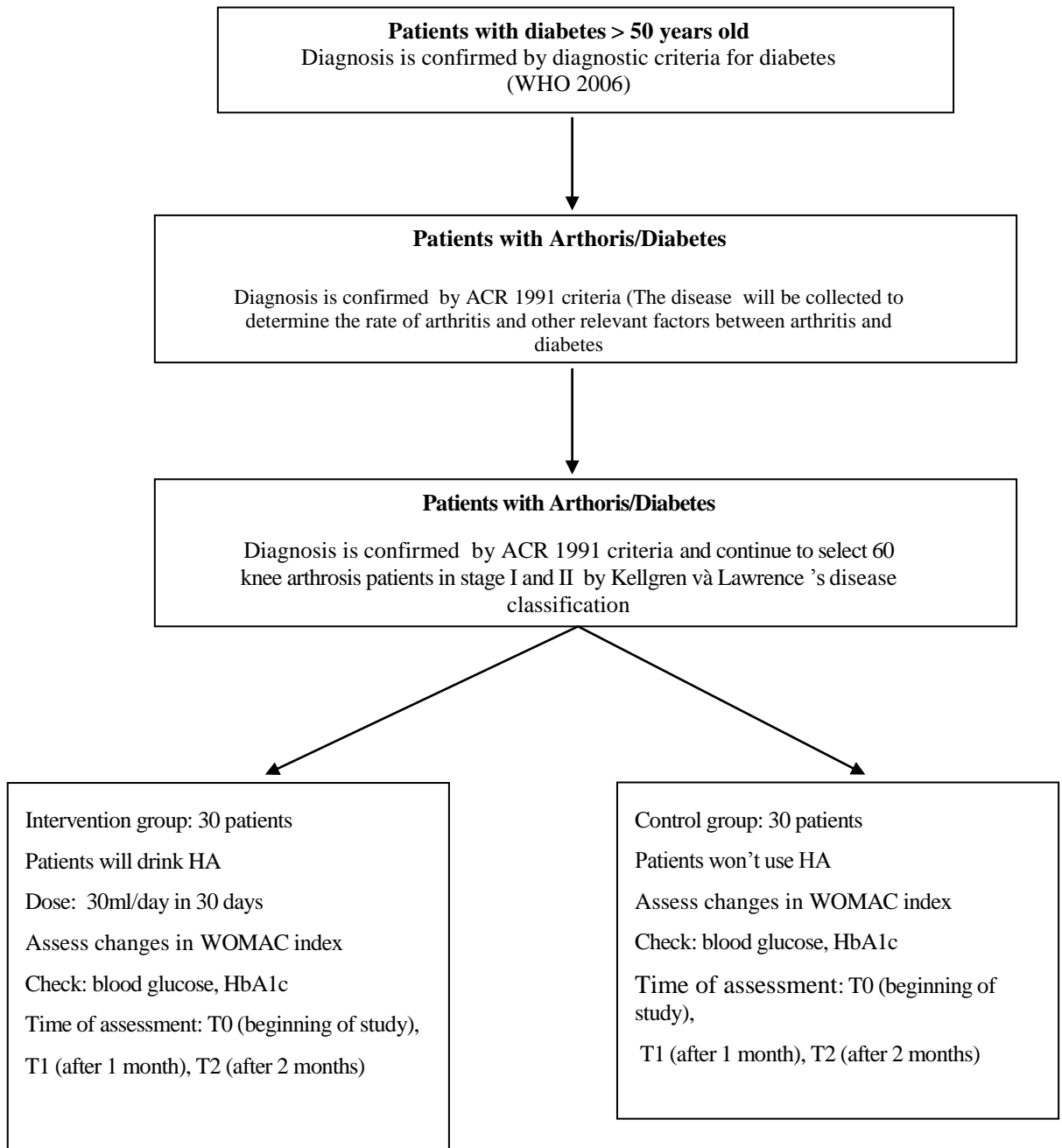
The algorithms are used:

- The percentage %.
- The average and standard deviation.
- Comparison of mean values before treatment and after treatment, mean values between groups by t-test, the rate %, difference2 test.

### **2.4. Ethic in study:**

- Have the permission of the hospital and the management board
- With the consent of the patient after explaining the meaning of specific research, the benefits and possible risks to patients. The study did not affect the rights of patients during treatment.

## Study Protocol

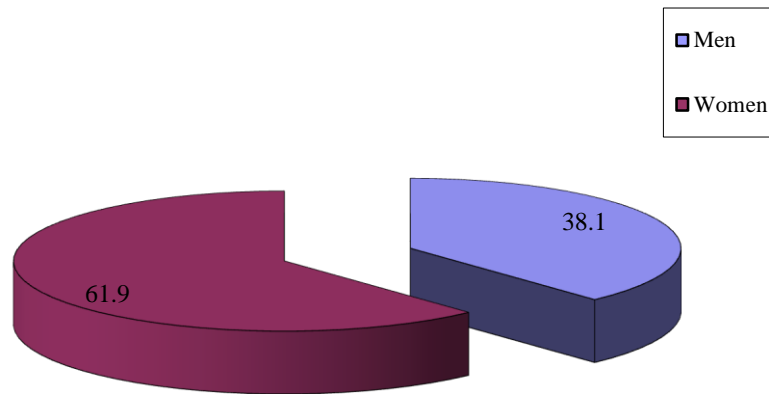


## CHAPTER 3

### RESULTS

#### 3.1. Some general features about the object of research:

- The number of patients studied : 270
- Sex distribution :           Women: 167  
                                           Men : 103



**Chart 3.1. Distribution of diabetes by gender**

**Table 3.1: Distribution Of Diabetic Patients by age,**

Age	Number of diabetic patients	%
50 - 59	39	14,4
60 – 69	128	47,4
70- 79	87	32,3

$\geq 79$	16	5,9
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*Comments:* The average age of elderly diabetic patients being treated at National Institute of Gerontology is :  $67.1 \pm 7.8$  years, which is most concentrated on 60-69 years old group.

**Table 3.2: Distribution Of Diabetic Patients by BMI**

<b>BMI</b>	<b>Number of diabetic patients</b>	<b>%</b>
> 23	149	55.2
18.5- 23	114	42.2
< 18.5	7	2.6

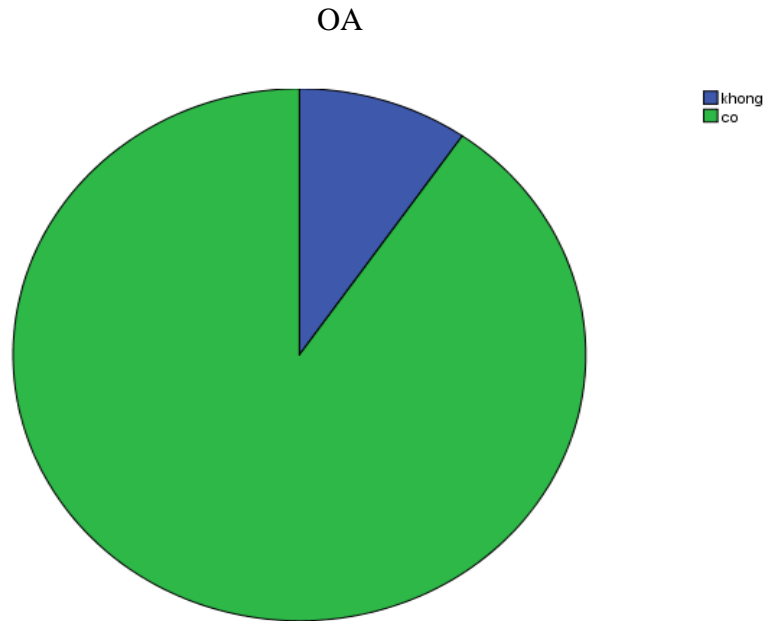
*Comments:* The rate of patients with type 2 diabetes occur more frequently in groups of overweight and obese patients ( 55.2% ) .

**Table 3.3: The rate of co-morbidities**

	<b>Number of patients</b>	<b>%</b>
High Blood Pressure	228	84.4
Lipid metabolic disorders	154	57.0
Gout	8	3.0
Cerebrovascular accident	16	5.9

*Comments:* The rate of patients which have hypertension is very high: 84,4% lipid metabolism disorders is 57.0%, accompanied by a small number of cerebrovascular (5.9%), gout (3.0%).

### 3.2. OA Problem of Diabetes Patients



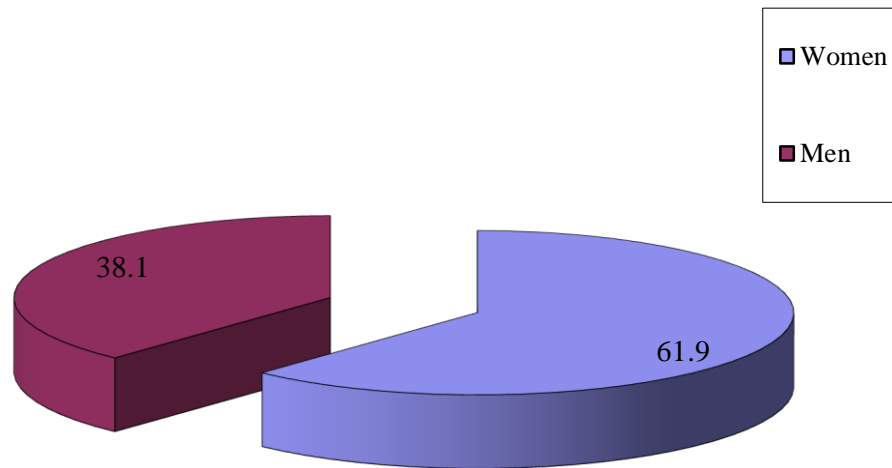
**Chart 3.2: The rate of patients who have knee OA**

*Comments:* The rate of type 2 diabetes patients who have knee OA is 90,4% (n = 270 patients)

**Table 3.4: The relationship between knee OA and gender in diabetes patients**

Gender	OA		OA rates
	Yes	No	
Women	151	16	90,4
Men	93	10	90,3

*Comments:* The rate of knee OA in women is :  $151/167 = 90,4\%$ , and the prevalence in man is  $90,3\%$ , this difference is not significant statistically with  $p > 0.05$



**Chart 3.3: The rate of OA in Diabetes patients ( By Gender)**

*Comments:* The rate of OA in type 2 diabetes occur more frequently in women (61.9%) than men (n = 244 patients).

**Table 3.5: The relationship between knee arthrosis prevalence and age**

Age	OA		Rate of having OA
	Yes	No	
50 - 59	33	6	84,6
60 - 69	115	13	89,8
70 - 79	80	7	92,0
$\geq 80$	16	0	100

*Comments:* The average age of OA patients was  $67,4 \pm 7,9$  years, the lowest is 51 years old and the highest is 92 years old. The higher the age the higher incidence of knee OA. Elderly people will get higher risk of having knee OA.

**Table 3.6: Characteristics of body mass index BMI**

<b>BMI</b>	<b>Number of patients</b>	<b>%</b>
Overweight	136	55,8
Normal	104	42,6
Underweight	4	1,6

*Comments:* Most patients have mass index  $> 23$  accounting for 55.8%

**Table 3.7: Biochemical characteristics in diabetes patients having OA**

<b>The Tests</b>	<b>The average value</b>
(FPG: <i>fasting plasma glucose</i> )	$6,8 \pm 2,1$ mmol/l
HbA1c	$6,1 \pm 0,7$ %
Cholesterol	$6,7 \pm 2,1$ mmol/l
Triglycerid	$2,1 \pm 1,2$ mmmol/l
HDL- Cholesterol	$1,1 \pm 0,2$ mmol/l
LDL- Cholesterol	$2,7 \pm 0,9$ mmol/l
Creatinin	$73 \pm 3,4$ $\mu$ mol/l
SGOT	$24,5 \pm 1,4$ U/l

SGPT	24,9 ± 1,4 U/l
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*Comments:* Most patients have blood glucose in well-controlled

In which : 23% of patients with increased Cholesterol

49,3% of patients with increased Triglycerid

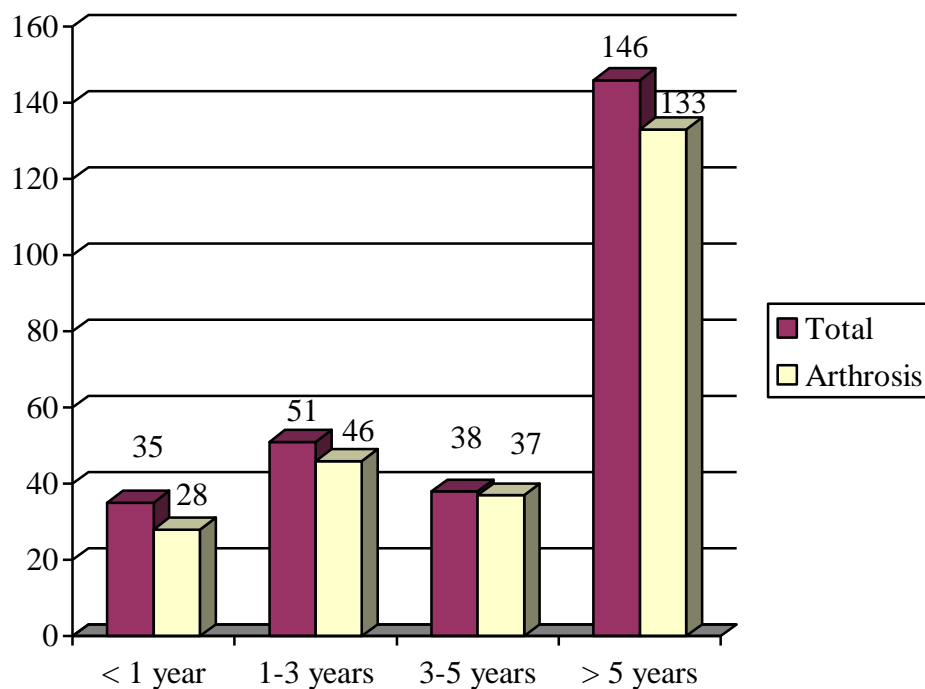
46,7% of patients with low HDL

24,8% of patients with increased LDL

3,3% of patients with renal failure

Most patients have normal liver function and blood glucose in well-controlled

### ***3.2.1. The relationship between some factors and OA in diabetes patients***



***Chart 3.4: The relationship between prevalence of knee OA and duration of finding diabetes.***

*Comments:* The rate of knee OA increases by the time that patients were found having type 2 diabetes, this difference was more evident among patients found diabetes under 1 year and over 5 years ( $p < 0.05$ ).

### 3.2.2. Some clinical symptoms of OA in diabetes patients

**Table 3.8: The duration of having OA (year)**

<b>Duration of disease</b>	<b>Number of patients</b>	<b>%</b>
≤ 1 year	29	11,9
1- 5 years	187	76,6
≥ 5 years	28	11,5

*Comments:* Most patients have the duration of disease from 1-5 years (66,6%)

The average time of patients having OA is  $2.5 \pm 2.9$  years.

**Table 3.9: Clinical symptom in hospital**

<b>Clinical Signs</b>	<b>Total (N = 244 patients)</b>	
	<b>n</b>	<b>%</b>
Knee Pain	206	84.4
Morning stiffness	36	14.8
Unusual noises (during movement of joint)	141	57.8
Limited range of joint motion	91	37.2

*Comments:* Most patients have sign of knee pain (84.4%) and unusual noises in joint (57.8%)

**Table 3.10: The effect of BMI to knee pain symptom**

	<b>No Pain</b>	<b>Pain</b>	<b>Total</b>
BMI > 23	15	119	134
BMI ≤ 23	23	85	108
Total	38	204	242

*Comment:* BMI can affect the symptom of pain with knee OA patients having  $p < 0.05$

**Table 3.11: Some clinical signs in hospital**

<b>Clinical signs</b>	<b>Total (N = 244 patients)</b>	
	<b>n</b>	<b>%</b>
Deformed joint	11	4,5
Stylosteophyte around the joint	0	0
Rheumatoid nodules	46	18,9
Joint effusion	8	3,3

*Comments:* 18,9% of patients have sign of rheumatoid nodules, 4,5% of deformed joint, 3,3% of joint effusion.

Table 3.12: OA position,

<b>OA position</b>	<b>Number of patients</b>	<b>%</b>
Right knee	109	44,7%
Left knee	29	11,9%
Both right and left knee	106	43,4%

*Comments:* The rate of right knee OA patients (44,7%) which is higher have statistically significant compared to the prevalence of left knee OA ( 11,9%) with  $p < 0,05$

**Table 3.13: Paraclinical features of OA in diabetes patients**

<b>Paraclinical features</b>	<b>Total (N = 244 patients )</b>	
	<b>n</b>	<b>%</b>
Inflammation syndrome	32	13,2
Stylosteophyte	220	90,5
Joint space narrowing	201	87,2
Solid bone under cartilage, flat the things under cartilage	216	88,9

*Comments:* Most knee OA patients have no inflammation syndrome (the rate of OA is 13,2%).

**Table 3.14: Classification of knee injury in radiograph by Kellgren-****Lawrence**

<b>Stage</b>	<b>Number of patients</b>	<b>%</b>
I	12	4,9
II	128	52,5

III	99	40,6
IV	5	2,0

*Comments:* Most patients have knee OA in stage II (52,5%) and stage III (40,6%)

### 3.3. The effect of oral-intake Hyaluronic in OA treatment for diabetes patients

*Table 3.15: Biochemical characteristics in 2 groups of knee OA patients*

LS-CLS Characteristics	Use HA	Control Group	p
Age	64,4 ± 7,8	63,6 ± 7,8	0,700
Duration of arthosis	2,4 ± 2,0	2,5 ± 2,4	0,665
Gender (men/women)	9/20	5/25	0,203
BMI	22,8 ± 5,3	23,1 ± 2,7	0,825
Waist measurements (cm)	89,3 ± 6,8	85,9 ± 7,5	0,074
Fasting plasma glucose (mmol/l)	6,4 ± 1,6	6,1 ± 1,1	0,511
Blood glucose after 2 hours of eating	11,3 ± 3,0	9,3 ± 1,3	0,165
HbA1c %	6,1 ± 0,7	6,1 ± 0,6	0,859
Leucocyte G/l	7,7 ± 2,1	7,4 ± 1,8	0,670

Duration of diabetes	5,2 ± 4,1	4,8 ± 3,9	0,625
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*Comments:* No differences in clinical and paraclinical features between 2 groups with  $p > 0.05$ .

**Table 3.16: Clinical symptoms of HA group were improved after treatment**

Clinical symptoms improved	HA		Control Group	
	Numbers of patients	%	%	%
Knee pain (n =28)	24	85,7	14	50
Morning stiffness (n =16)	12	75,0	7	46,7
Limited range of joint motion (n =28)	26	92,8	15	53,6

*Comments:* The rate of knee pain patients who have improvement in intervention group is 85,7% compare to 50% of control group as well as the sign of morning stiffness is 75,0% when the control group is 46,7% . Patients have improvement in range of joint motion is 92,8%.

**Table 3.17: WOMAC index of HA group were improved after treatment**

Womac index	T0	T1	T2
The total average	44,6 ± 18,3	26,4 ± 17,0	24,5 ± 14,8
A	8,5 ± 3,5	4,4 ± 2,8	3,7 ± 2,6
B	1,4 ± 1,7	0,5 ± 0,9	0,4 ± 0,7
C	35,7 ± 14,4	21,6 ± 12,7	20,4 ± 12,3

*Comments:* Womac score after treatment were decreased have statistically significant with  $p < 0,05$

**Table 3.18: Womac index of control group in difference time**

<b>Womac index</b>	<b>T0</b>	<b>T1</b>	<b>T2</b>
The total average	39,3 ± 16,2	35,0 ± 14,3	34,7 ± 14,0
A	8,7 ± 3,8	7,9 ± 3,4	7,5 ± 3,2
B	1,2 ± 1,5	0,9 ± 1,2	1,0 ± 1,3
C	29,4 ± 12,7	26,4 ± 11,0	26,0 ± 10,8

*Comments:* Womac score of control group after the first month of treatment was significantly reduced compared to the original, but there is no difference between the first month and 2 months.

**Table 3.19: Womac index between the 2 groups at the beginning of the study****T0**

<b>Womac index</b>	<b>HA</b>	<b>Control group</b>	<b>P</b>
The total average	44,6 ± 18,3	39,3 ± 16,2	0,242
A	8,5 ± 3,5	8,7 ± 3,8	0,634
B	1,4 ± 1,7	1,2 ± 1,5	0,806

C	35,7 ± 14,4	29,4 ± 12,7	0,105
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*Comments:* No differences about Womac index between the 2 groups at the beginning time of study T0 (no intervention) with  $p > 0.05$

**Table 3.20: Womac index of 2 groups after 1 month of using HA ( T1)**

<b>Womac index</b>	<b>HA group</b>	<b>Control group</b>	<b>P</b>
The total average	26,4 ± 17,0	35,0 ± 14,3	0,037
A	4,4 ± 2,8	7,9 ± 3,4	0,000
B	0,5 ± 0,9	0,9 ± 1,2	0,137
C	21,6 ± 12,7	26,3 ± 11,0	0,109

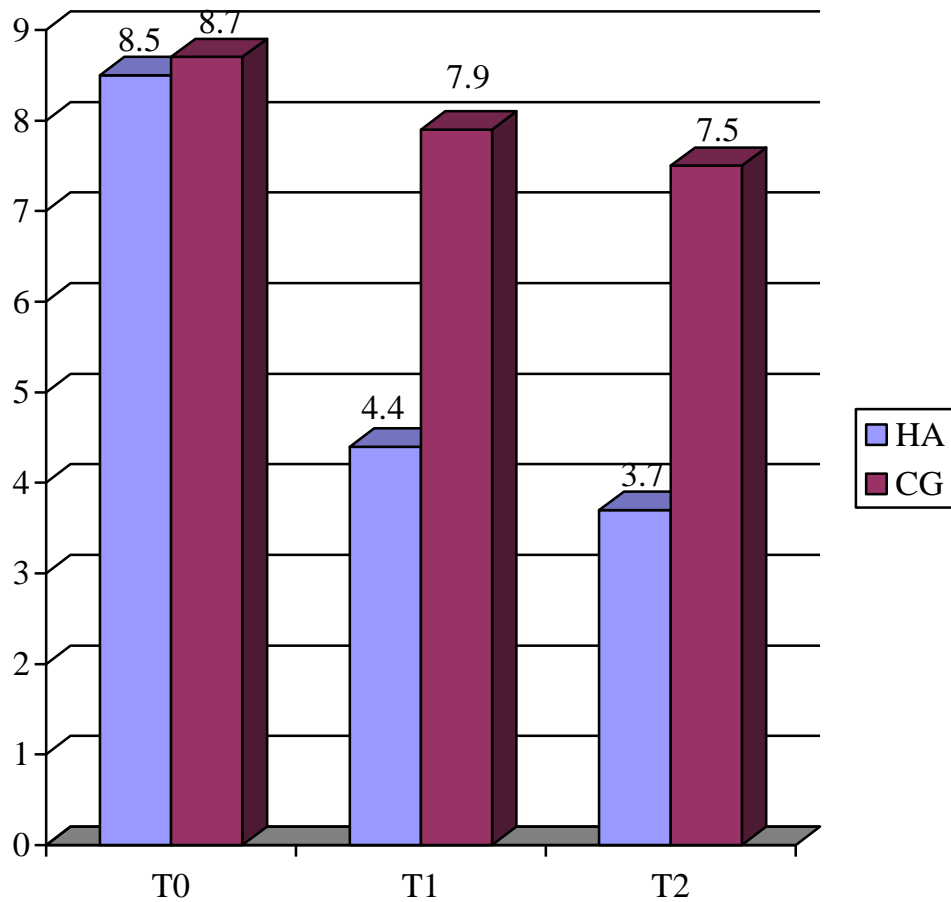
*Comments:* After 1 month of using oral intake HA , the total average Womac index and Womac A of HA group were significantly reduced compared with control group

**Table 3.21: Womac index of 2 groups after 2 months of using HA (T2)**

<b>Womac index</b>	<b>HA group</b>	<b>Control group</b>	<b>P</b>
The total average	24,5 ± 14,8	34,7 ± 14,0	0,011
A	3,7 ± 2,6	7,5 ± 3,2	0,000

B	$0,4 \pm 0,7$	$1,0 \pm 1,3$	0,026
C	$20,4 \pm 12,3$	$26,0 \pm 10,8$	0,078

*Comments:* After 2 months of using oral intake HA , the total average Womac index and Womac A and Womac B of HA group were significantly reduced compared with control group ( $p < 0,05$ ).

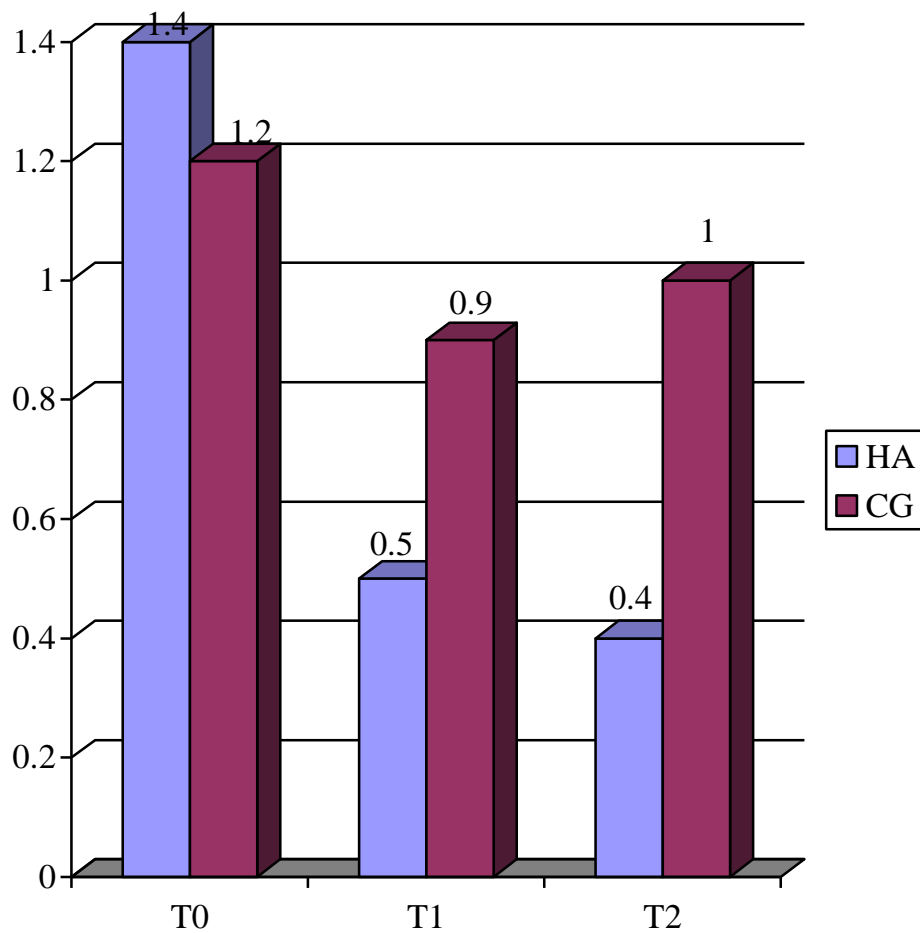


**Table 3.5: Evaluate the changes of pain symptom (WomacA) in 2 groups**

*Comments:* Womac A index decrease more clearly in intervention group than control group

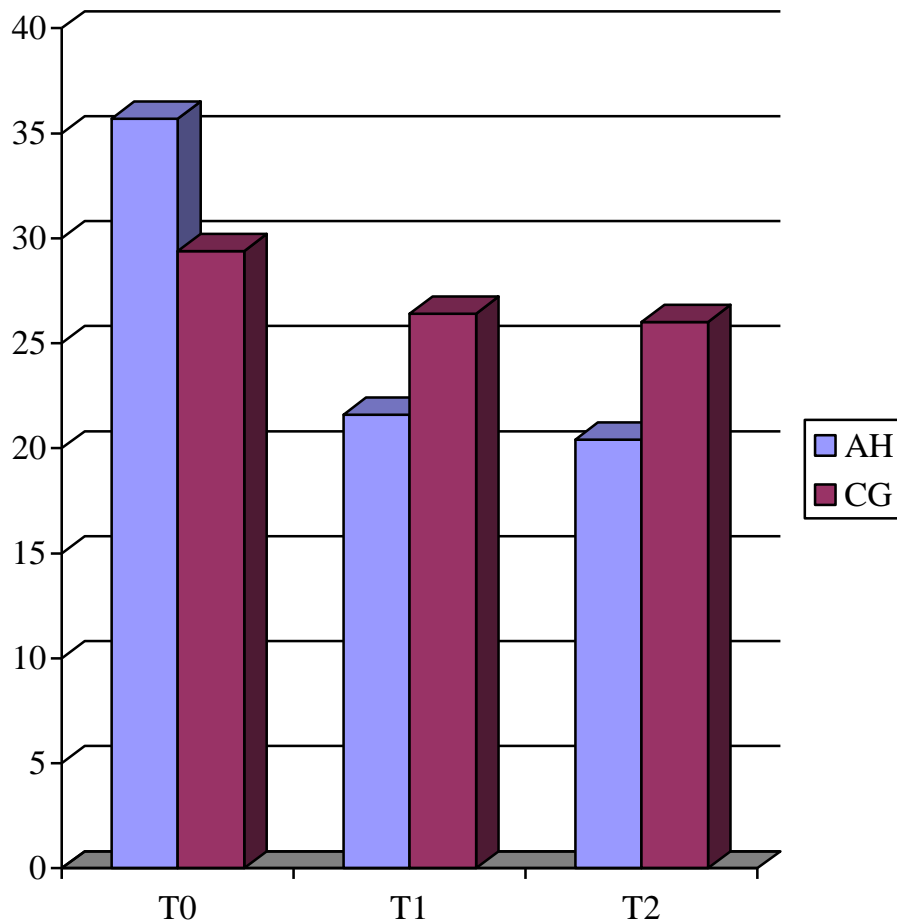
T1: The intervention group decreased 47,8%, control group is 8,6% reduction

T2: The intervention group decreased 55,7%, control group is 14,1% reduction



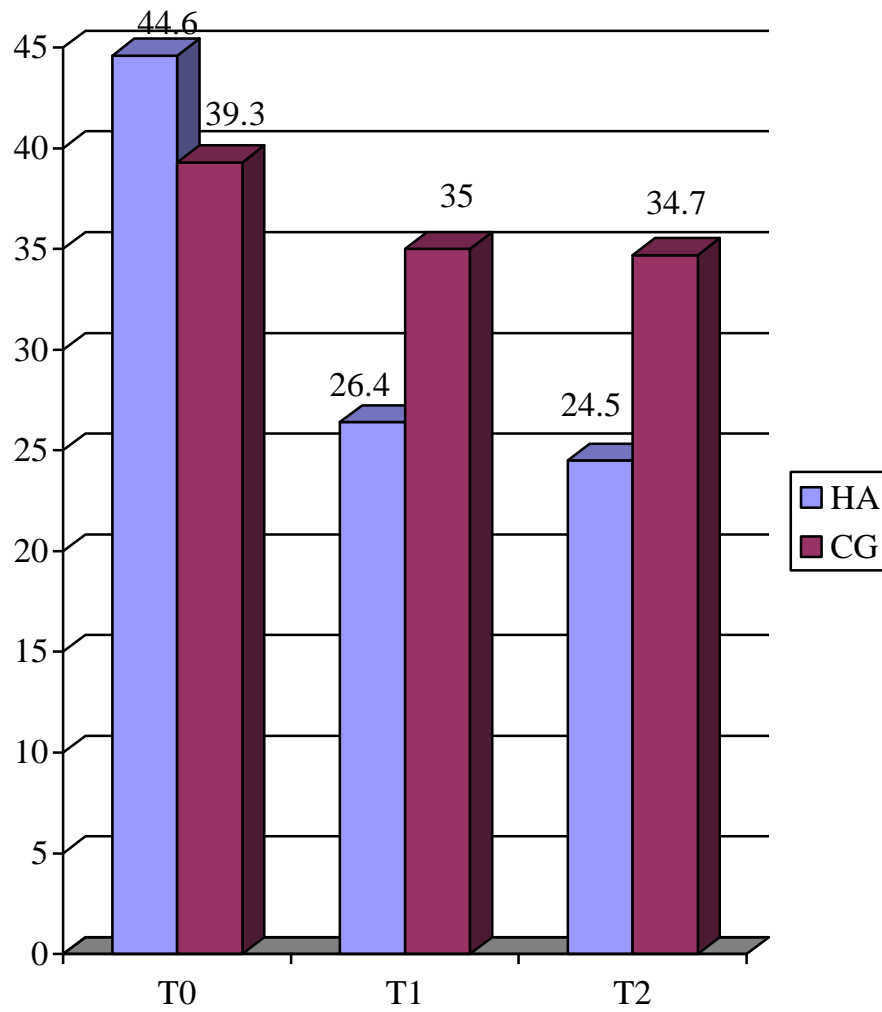
**Table 3.6: Evaluation of changes in the Womac B index of 2 groups**

*Comments:* The reduction of Womac B index in intervention group is very strong at T1 ( 60,9% reduction ) and continued decrease at T2 ( 73,9% reduction).



***Table 3.7: Evaluation of changes in the Womac C index of 2 groups***

*Comments:* Womac C index of the 2 groups were reduced but HA group has clearer expression: 39.4% reduction in T1, T2's decrease was 42.2% compared with T0.



***Table 3.8: Evaluation of changes in the average Womac index of 2 groups***

*Comments:* After 2 months of monitoring, the total average Womac score in both 2 groups were decreased but HA group is more than intervention group.

**Table 3.22: HbA1c index, fasting glucose, glucose after 2 hours of eating and treatment**

<b>Index</b>	<b>T0</b>	<b>T3</b>	<b>P</b>
Fasting glucose	6,3 ± 1,6	6,4 ± 1,4	0,786
Glucose after 2 hours of eating	11,4 ± 3,7	11,1 ± 2,8	0,801
HbA1c	6,1 ± 0,8	6,0 ± 0,7	0,633

*Comments:* No changes about the fasting glucose, glucose after 2 hour of eating and HbA1c before or after using HA orally with  $p > 0,05$ .

**Table 3.23: Unwanted effects of Hyaluronic Acid for oral intake**

Unwanted effects	Number of patients	%
Mild allergic	1	3,3%
Weight gain (2kg/2 weeks)	1	3,3%

*Comments:* Unwanted effects of HA: 6,6%, Mild allergic is over when the patients stop drinking .

## **Chapter 4**

### **Discussion**

#### **4.1. General characteristics of examined patients:**

##### ***4.1.1. Age and Gender of examined group:***

According to the results of our study , the average age of type 2 diabetes patients who have outpatient treatment at National Institute of Gerontology (NIG) is  $67,1 \pm 7,8$  years. 60-69 years old group accounted for the highest rate : 47,4%,the lowest age is 51 years old and the highest is 92 years old. According to research by Catherin C [39], the rate of diabetes increased about 21,6% at the ages of 65 and older. As annouced by WHO, the rate of diabetes in older adults is about 8-15% [76]. Our average age is higher than other studies because the characteristics of hospital is the treatment for elderly.

About Gender : the prevalence of femaly patients in our study is 61,9%. It has statistically significant ( $p < 0,05$ ) and higher than the male prevalence who is currently treated at the National Institute of Gerontology.

##### ***4.1.2. The anthropometric indicators of elderly patients with diabetes***

Overweight and obesity are the risk factors of insulin resistance and diabetes type 2. The results of our study show that the average BMI among patients being treated at NIG is  $23,4 \pm 3,2$ , the percentage of overweight and obesity ( $BMI > 23$ ) accounted for the highest rate ( 55,2% ). Abdominal obesity is also one the the risk factors of type 2 diabetes, the rate of patients with high waist circumference (men $>90$  cm, women  $>80$  cm) is 67,8% ( 51,1% female, 16,7% male ), the average waist index is  $87,4 \pm 7,4$ cm.

The rate among patients with hypertension is 84,4% including 27,1% patients who have good control at blood pressure. 72,9% Systolic blood pressure > 130mmHg. The patients group have lipid metabolic disorders occupied a high rate ( 57%), and other diseases such as: Gout ( 3% ) , Cerebrovascular accident ( 5,9%).

#### **4.2. Knee OA problem in elderly diabetic patients**

The prevalence of having knee OA in elderly diabetic patients 90,4% in our study. According to reserch by Nguyen Thi Nga and colleagues, [17] In 406 people work in agriculture ( over 40 years old ) the rate of knee OA is 32,5%. While the rate of knee OA in the U.S.A ( over 60 years old) is 40% [60]. Thus, we found that the prevalence of having knee OA in diabetes patients ( over 50 years old ) have statistical significance higher than the rate of OA in elderly general. Gregory's research [49] in USA show that 80-90% people over 65 years old have symptoms of knee OA .

##### **4.2.1. Gender characteristics**

Both the two sexes may have OA or knee. Previous studies in Viet Nam and the world showed the rate of having knee OA is much higher in women than men . The results of our study show that the rate of OA in women is 61,9% higher than men (38,1%).In there, the rate of having knee OA in diabetes women patients is 90,4% and men is 90,3%. The difference about the prevalence of having knee OA in diabetes patients ( both two sexes) has no statistically significant with  $p > 0,05$ .

This result is different than previous studies . As in Nguyen Van Pho study of 151 patients with knee OA have medical treatment in rheumatology at Bach Mai hospital , the rates of male : femaly is 1:6 [20]. This rate in Saranatra study [67] of 40 patients with knee OA is 1:5 in Thailand.

According to Huskisson and colleagues [52] in USA, the study on 100 OA patients has the rate of women is 76%.

Thus the results of our studies is different than other reseach because we study on elderly diabetes patients who have the high rate of OA and no differences between 2 sexes

#### ***4.2.2. Age characteristics***

The average age of knee OA patients in our study is  $67,4 \pm 7,9$  years old, most patients  $> 60$  years accounted for 86,5%. Patients with knee OA have the highest age is 92 and the lowest is 51 . This rate is consistent with other studies. As in the study of Nguyen Van Pho [20] have average age is  $63,2 \pm 10,0$  years old, the rate of patients  $> 60$  years is 62,3%. Another study in Thailand [67] of 40 knee OA patients have average age is  $64,2 \pm 3,0$  years old. The knee OA patients in Europe, America also has an average age over or under 60 years old. The study of Brand in Sweden [35] showed that the average age of knee OA is  $65 \pm 8,4$  years old.

Age problem is also one of the favorable factors of knee OA . Therefore, that is one of the main factor for OA diagnostic criteria in ACR 1991( age of patients  $> 40$  years). Elderly people will get higher risk of having knee OA. The rate of knee OA in type 2 diabetes patients  $> 60$  years is 91,3% higher and have statistically significant compared with the prevalence of patients  $< 60$  years (84,6%) with  $p < 0,05$ , this rate is higher than the prevalence of knee OA in patients ( farmer)  $> 60$  years (44,7%) in the study by Nguyen Thi Nga [17].

#### ***4.2.3. Characteristics of body mass index (BMI)***

Studies by many authors have found that the role of BMI affect OA,especially for the knee joint which has to bear the whole body weight. The body that has obesity and overweight will cause OA for earlier and worse. The

risk of having knee OA in obese people is higher 7 times than normal [35]. Research of knee OA in Thailand by [67] ( 40 patients) showed the rate of obese people is 67,3%. According to research by Zeng Qing Yu and colleagues [78] on 2188 Chinese patients showed the average BMI in knee OA group is  $25,3 \pm 3,1$  compared with  $22,7 \pm 3,1$  in group with no OA (  $p < 0,01$  ) . OA group in the study of Patrella and colleagues in Canada [62], Goupille P in France [47] have an average BMI of 31.

Nguyen Van Pho research [20] in 151 knee OA patients at Bach Mai hospital ( 2007 ) showed that the average BMI is  $23,3 \pm 3,1$  ( The group of patients that are overweight, obesity accounts for highest is 52.3%)

The results of our study show that the average BMI in patients with type 2 diabetes having knee OA is  $23,3 \pm 3,2$ , and the percentage of overweight and obese patients accounted for the highest rate is 55,8%. We also found that BMI affects the pain expression of patients with  $p < 0,05$ . Patients group with BMI  $> 23$  have joint pain symptoms more than the group with BMI  $\leq 23$  (table 3.12). Our average BMI index is lower than oversea studies but similar to studies of Nguyen Van Pho in Viet Nam , this difference is due to the unlikeness of Vietnamese anthropometric characteristics and the examined patients has type 2 diabetes.

#### ***4.2.4. Biochemical characteristics of knee OA patients with type 2 diabetes***

Most knee OA patients with type 2 diabetes are treated in NIG have blood glucose under control, expressed in average blood glucose of this group is  $6,8 \pm 2,1$ mmol/l, the average HbA1c is  $6,1 \pm 0,7\%$ . But the index of blood lipid is higher than normal, Average Cholesterol is  $6,7 \pm 2,1$ mmol/l,

Average Triglycerid is  $2,1 \pm 1,2$ mmol/l. Most patients have liver and kidney function in normal ,3 % of patients with renal manifestations.

#### ***4.2.5. The relationship between the duration of finding diabetes and OA***

Do the duration of finding diabetes and the rate of having OA truly connect with each other? This also is a problem we want to mention . According to our analysis, we found no difference between the rate of knee OA patients who got diabetes < 1 year, 1-3 years, 3-5 years, > 5 years ( $p > 0,05$ ). But this rate is clearly different in patients who newly discovered diabetes (< 1 year: 80%) and patients who found having diabetes in long-term (> 5 years: 91,4%), the difference is statistically significant  $p < 0,05$  . Therefor diabetes has strong connection with knee OA.

### **4.3. Some main clinical symptoms of knee OA in type 2 diabetes elderly patients**

#### ***4.3.1. Time of having knee OA***

OA is a disease of chronic evolution, causing pain and joint deformities and often haven't signs of inflammation. The main cause of disease are aging and overload of articular cartilage [2]. Paraclinical feature is just mild pain, pain when moving and reduced after resting. In long-term this will make the effect on joint movement function . Therefore, knee OA patients just come to

hospital when have severe pain or knee joint function is affected. This is the reason why the time of having disease is long.

The results of research show that time of having knee OA in type 2 diabetes patients is  $2,5 \pm 2,9$  years, including the highest rate of having OA from 1-5 years is 76,6%, patient was found OA is 20 years ( oldest) . The average time of having knee OA in our study is lower than in the research of Nguyen Van Pho ( $4,3 \pm 2,7$ ) [20] with  $p = < 0,05$ . Our examined patients is type 2 diabetes could be the reason why it happened. Most patients have unclearly clinical symptoms and having no complain in hospital about their health. Many patients know about the knee OA in research time (new patients found is 11,9%). According to research by Brandt and colleagues in USA[36], the average time in patients who have knee OA is  $3,0 \pm 3,5$  years.

#### ***4.3.2. Clinical Symptoms***

Knee OA is a disease of chronic evolution , the initial signs is joint pain, increasing pain when moving. Patients will feel better when have a rest or use some normal analgesic. Furthermore, the object of our research is diabetes patients and sometimes they do not talk to doctor about the expression of discomfort in their joints. This may explain why the rate of knee pain in knee OA patients in our study was 84,4% , not 100%. 15,6% patients were found at the time of research have no signs of knee pain .The rate of patients have

unusual noises in knee joint is 57,8% and this is also a common clinical symptom of knee OA patients. 38% people have effect on range of knee joint motion BN, a few have signs of morning stiffness (14,8%). Clinical symptoms examination at the beginning of research showed : about 18,9% patients have sign of Rheumatoid nodules, 4,5% of Deformed joint, 3,3% of Joint effusion.

#### ***4.3.3. Position of degeneration***

Knee joint is one of the position has to bear the whole body weight so it's easy to be degenerate. In the early stage, the clinical symptoms of knee OA is unclear. Sometimes it's just a tired feeling at knee joint , have pain in one knee first and both knees after. According to the results of our study showed that 43,4% patients have symptom of OA in both knees, the rate of right knee OA (44,7%) is significantly higher than the prevalence of left knee OA (11,9%) with  $p < 0,05$ . May be the right knee is often-used joint so it has a higher activity levels and bears more weight than left knee. It can brings the degeration of joint sooner . Nguyen Van Pho research in 151 knee OA patients at Bach Mai hospital showed the prevalence of OA in both knees is 68,2%, the rate of right knee OA is higher than left knee (20,5% compared to 11,3%) [20].

#### ***4.3.4. Characteristics of x-rays***

Although there are many new methods of diagnostic imaging applications such as CT or MRI scanner nowadays, the x-ray with knee in straight- tilt posture is the main image method used to dianose and assess the vulnerability of knee OA. This is a simple method, high efficiency, cheap and easy to implement. Degenerative joint injury with loss of cartilage and bone regeneration activities under the cartilage are usually represented by the “ joint space narrowing ”, stylosteophyte and Osteoporosis under the cartilage .

In case of OA progressing , we can see some holes in epiphyseal process under the cartilage.

Patients in our research are knee OA people in type 2 diabetes ( > 50 years old ). Most patients have knee OA in stage II or III according to Kellgren-Lawrence classification. The image of joint injury on X-ray shows most of knee OA damage : 90,5% of patients has BN bone regeneration activities, 87,2% with joint space narrowing from less to more, 88,9% with image of solid bone under cartilage. Most knee OA patients are in Kellgren stage II (52,5%) and III (40,6%) . 4,9% patient is in stage I and 2,0% in stage IV .

#### **4.4. The effect of hyaluronic acid (HA) for oral intake in knee OA treatment of type 2 diabetes elderly patients**

To evaluate the effect of HA in knee OA treatment for type 2 diabetes patients, we selected two type 2 diabetes groups which have knee OA . They all have nearly same paraclinical and clinical feature (table 3.16), 100% patients have knee OA in Kellgren stage 2. In this study we used the Womac index to assess pain, stiffness and range of knee motion

##### ***4.4.1. Evaluate the effect of treatment through joint pain levels***

Joint pain is usually the first clinical symptom of OA. The pain has mechanical properties which means the feeling of pain when moving and reduced after resting. In first stage, patients will feel pain when they carry heavy things , climb stairs, stand up or sit down and squatting... the pain levels increased after that. Patients may feel knee pain in movement, walking on the normal road and even in resting time . Patients may feel pain naturally, after walking a distance or start moving , more severe pain make the patient have to use crutches. Womac index was used to evaluate the pain levels ,

stiffness and range of knee joint motion. At the beginning of study ( TO), the average pain level of patients in HA group is  $8,5 \pm 3,5$  points, the control group is  $8,7 \pm 3,8$  points. There is no difference in pain level between 2 groups ( $p = 0,634$ ).

Table 3.19 shows that at the beginning of the study, the level of pain, stiffness and motor functions of the two groups is the same with  $p > 0.05$ . The degree of pain was significantly improved in the HA group (Table 3.19) after the first month (from  $8.5 \pm 3.5$   $4.4 \pm 2.8$  decreased with  $p < 0.05$ ) and was maintained within 2 months (average pain intensity in this group is  $3.7 \pm 2.6$ ).

The Table 3.20, Chart 3.5 shows that the average pain level decreased significantly in HA group and the differences compared with control group with  $p < 0.05$ . The level of pain among patients with HA decreased 47.8% compared with 8.6% in the control group after one month decreased 55.7% compared to 14.1% in the 2nd month. Number of patients with improved symptoms is 85.7% in HA groups while in the other group only 50% of patients have decreased pain.

#### ***4.4.2. Assessment on effectiveness via signs of stiffness and pain***

Sign of stiffness and pain in joints is a common symptom in OA especially in knee OA, it often occurs when waking up or when warming up after a long rest, the patients often have difficulties in moving but after a few moves, the signs start losing. According to the results of our study, the level of Sign of stiffness and pain in joints was assessed by Womac B. At the start of the study, the average score of the 2 groups was:  $1.4 \pm 1.7$  (in HA group) and  $1.2 \pm 1.5$  (control group), there is no difference between the 2 groups with  $p = 0.806$ .

The results in Table 17.3 shows signs of stiffness and pain in joints were significantly improved in patients taking HA with average Womac B from  $1.4 \pm 1.7$  (T0) to  $0.5 \pm 0.9$  (T1), down 60.9%, reduced to  $0.4 \pm 0.7$  at the time T2, down 73.9%

Table 3.20 and 3.21 shows the average Womac B of two groups after 1 month of treatment without difference ( $0.5 \pm 0.9$  and  $0.9$  in intervention group,  $\pm 1.5$  in control group) with  $p = 0.137$ . But after the 2nd month, the Womac B changed:  $0.4 \pm 0.7$  in the intervention group compared with  $1.0 \pm 1.2$  ( $p$ -value = 0.026). Chart 3.6 also shows the change in the intervention group: decreased 1.0 points after 2 months of treatment, whereas in the control group: only 0.2 points.

#### ***4.4.3. Assessment of effectiveness via treatment of motor function of knee joint***

Limited knee motion in knee OA is often due to various factors such as pain, loss in quality and quantity of hyaluronic acid molecules in joint fluid (leading to decreased function of fluid such as lubricating properties, elasticity...), inflammation of the synovial membrane, including joint injuries, cartilage loss, joint space narrowing. Motor function of the joint is evaluated through the ability of walking, climbing stairs, squatting, shopping, up and down and so on is one of the criteria of Womac C. At the start of the study (T0), average Womac C of 2 groups did not differ (intervention group was  $35.6 \pm 14.4$ , control group was  $29.4 \pm 12.7$ ) with  $p = 0.105$ .

The results in Table 18.3 showed the motor function of the knee joint of the intervention group was significantly improved is reflected in the decline from  $35.6 \pm 14.4$  Womac C at the start of the study (T0) to  $21.6 \pm 12.7$  after 1 month of treatment (T1) and  $20.4 \pm 12.3$  after 2 months (T2) with  $p < 0.05$ .

In table 3.20 and 3.21, the result showed the average Womac C of the two groups after the 1st and 2nd month without difference with  $p = 0.109$  (T1),  $p = 0.078$  (T2). But look at the chart 3.6 Womac C fell in the intervention group and control group without difference. Womac C in the group that uses HA decreased from  $35.6 \pm 14.4$  to  $21.6 \pm 12.7$ , reduced by 14.1 (down 39.4%) compared with control group: reduced 3.0 (10.2%) at T1, it continues down 1.2 at T2 (ie, declining 42.2%) while the control group decrease 0.4 (ie 11.4%). Thus, although the two groups of Womac C at 2 times T1, T2 have no difference, the intervention group tended to reduce the Womac C than the control group.

#### ***4.4.4. Evaluating the effect of treatment by general WOMAC***

Pain of OA is known by many mechanisms such as inflammation of the synovial membrane, joint bursitis, stretch of nerve endings in the periosteum because of stylosteophyte, small bone cracking under the cartilage brings the irritation. Pain and changes of structure in OA lead to the decrease of joint's range motion. Moreover, the damage of cartilage, the reduction of synovial fluid, inflammation of capsular ligament, synovial membrane and the degeneration around the joints show the symptoms of morning stiffness. Patients become disabled in many cases. Womac index was used to evaluate the pain levels, knee stiffness and range of knee joint motion. At the beginning of research, there is no difference in total average Womac index of 2 groups ( $47,6 \pm 18,3$  in intervention group,  $39,3 \pm 16,2$  in control group) with  $p = 0,242$ .

The results in table 3.17 shows that the average Womac index of HA group after the first month was decreased significantly ( from  $45,6 \pm 18,3$  in T0 down to  $26,4 \pm 17,0$  in T1), about 42,0% compared with the beginning

time and it continues to decrease about 46,1% after the second month. Compared with the control group in table 3.22, the average Womac index of intervention group was lower than control ( $35,0 \pm 14,3$ ) has the statistically significant with  $p = 0,037$ . Compared with control group at T2, our result show that the total average Womac index of intervention group is lower than control group ( $24,5 \pm 14,8$  in HA group and  $34,7 \pm 14,0$  in control group) has statistically significant with  $p = 0,011$ .

The result in Figure 3.8 shows that the average Womac index in intervention group was decreased and it was more clear than control group. After the first month, the average Womac index of intervention group decreased 18,2 points (42%) while the control group was 4,3 point (10,8%). After the second months, the average Womac index of intervention group continues to decrease 1,9 point again (it means 46,1% compared to T0) and control group decreases 0,3 point ( 11,7% compared to T0).

#### ***4.4.5. Evaluating the effect of HA to blood glucose control***

Blood Glucose Control (BGC) still is a challenging problem for the therapist. To be on the diet, exercises and having medicine everyday are not always seriously and fully taken by the patients. This has been demonstrated in patients with type 2 diabetes when they have joints problem . Therefore , doing exercises and drug therapy will become more difficult for patients. According to research by Reginster JY [65], high doses of glucosamine treatment will affect blood glucose. The problem here is: type 2 diabetes patients who have knee arthrosis used HA affect blood glucose of patients or not ? The results in Table 3.22 showed there is no difference in HbA1c, fasting glucose, blood glucose after 2 hours of eating between groups who used HA after and before the treatment with  $p > 0,05$ .

#### ***4.4.6. Unexpected effect of HA***

During researches, we found that two patients withdraw from the study: 1 patient with mild allergic manifestations in the form of itching or rash on the skin, this stopped after patients stopped all medications a day, this patient has a medical history of allergic with honey so this issue can be caused by by components of honey in the HA product; 1 patient gained weight after 2 weeks of drinking HA (increase of about 2 kg). The remaining patients did not show any adverse reactions.

## CONCLUSION

### 1. Situation of knee OA in aged patient with diabetes type 2

Study 270 patients with type 2 diabetes > 50 years old at outpatient Department of NGI showed that the knee OA rate was 90.4% among patients, average age of patients with knee OA was  $67.4 \pm 7, 9$ , duration of disease was  $2.5 \pm 2.9$  years, without difference in incidence between the two genders. Clinically, 84.4% of patients have pain in knee, most of patients have knee OA patients at Kellgren II (52.5%) and Kellgren III (40.6%).

### 2. Effectiveness of oral HA in treatment of OA for aged type 2 diabetic patients

- Symptoms of pain: The Womac A of 4.8 in reduction in the intervention group from  $8.5 \pm 3.5$  at T0 to  $3.7 \pm 2.6$  at T2, while the control group only lost 1.2. Number of patients with knee pain decrease was 24 patients accounting for 85.7%.

- There were 12 patients out of 16 patients with signs of stiffness and pain in joint improved (accounting for 75%), Womac B in the intervention group was 1.0 lower after 2 month of follow-up compared with the control group with drop of only 0.2

- The motor function of the knee joint: 92.8% patients improved in motor function of knee, Womac C decrease 15.3 in the intervention group compared to control group with only 3.4 decrease

\* The effects were observed after 1 month of treatment and lasted 2 months

## **RECOMMENDATIONS**

Based on study results, we have some recommendations as follows:

- It is better to take radiographic image of knee in patients with diabetes > 50 years old for guidance on consistent training regimen for each patient.
- It is better to take oral HA from the very beginning of OA

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