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Non-Insulin Dependent Diabetes Mellitus (NIDDM) Profile in Nablus District, Palestine

By

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This Work is Fully Dedicated to
my Parents
Wife
and kids

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Abstract

The profile of non- – insulin dependent diabetes mellitus (NIDDM) in Nablus district was investigated. NIDDM patients n=323 were selected from three diabetic clinics.

Although the study included 49 non- diabetic people, but its not considered as control case study.

Both NIDDM and non- diabetic populations were obese as reflected by body mass index > 30 kg/m^2. Total cholesterol and triglycrides in NIDDM were higher than normal range, while HDL – cholesterol was significantly lower than normal. Women with NIDDM showed a higher BMI and HDL-cholesterol than diabetic men. Systolic blood pressure increased with increasing age. NIDDM people living in the refugee camp showed higher BMI and systolic blood pressure and lower levels of total cholesterol and LDL-cholesterol than NIDDM people living in the city or village.

Non-diabetic people living in the refugee camp showed higher HDL-cholesterol and lower LDL-cholesterol levels than non-diabetic individuals living in the city.

81% of NIDDM population have parental history of diabetes. This ratio decreased with increased aging to reach 62% at 60 years old group.

Chapter I
INTRODUCTION

Diabetes mellitus has been known for several centuries (1,2). Our knowledge of the nature of diabetes is still incomplete. Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action.

Diabetes mellitus may be recognized clinically by the presence of characteristic symptoms such as excessive thirst, polyuria, blurred vision, recurrent infection, excessive hunger, profuse urination and weight loss or weight gain. Coma and death can occur in advanced or untreated conditions.

1.1 Classification of Diabetes Mellitus:

The most widely adopted classification of diabetes mellitus was suggested initially by the National Diabetes Data Group (NDDG) in the United States and subsequently became the basis for the World Health Organization (WHO) (3,4). Previous classification of diabetes was based on patient's insulin dependency (5). Currently, both the American Diabetes Association (ADA) and the WHO are classifying diabetic patients into four defined subtypes (6,7).

Insulin Dependent Diabetes Mellitus (IDDM)

IDDM is due to auto-immune disease or idiopathic forms of cell dysfunction which lead to absolute insulin deficiency. The vast majority of patients have measurable concentration of auto-antibodies in their blood (8).

Non –Insulin Dependent Diabetes Mellitus (NIDDM)

NIDDM is mainly due to insulin resistance or relative deficiency (9).

Gestational Diabetes

This form is usually observed during pregnancy (10).

Impaired Glucose Tolerance

Is not diabetes mellitus, *per se*, but describes glucose tolerance outside the range normally found in young and healthy adult (3).

Other types of diabetes

Covers a wide range of specific conditions and syndromes including various genetic defects of cell function, insulin action and disease of exocrine pancreas (3).

1.2 Criteria for Diagnosis

The clinical diagnosis of diabetes is often suggested by the presence of classical hyperglycemic symptoms such as excessive thirst and glycosuria, sometimes with drowsiness or coma. If so,

the diagnosis can usually be confirmed by using fasting blood or plasma glucose determinations without provocative tests.

The American Diabetes Association (ADA) has recently proposed to use fasting plasma glucose (FBG) only for the diagnostic purposes, and they suggested the lowering of the threshold to 126mg/dl (11). WHO consultation has accepted the new threshold, while retaining the oral glucose tolerance test (OGTT) as a standard diagnostic procedure (5). These diagnostic criteria are applied for gestational diabetes.

1.3 Etiology of Diabetes

The etiology of diabetes is not fully understood, but in general, genetic, environmental and lifestyle factors are thought to interact in the occurrence of the disease.

Since the present study focuses on NIDDM, the following will deal with the relevant materials.

1.3.1 Genetic Factors

For type I diabetes genetic factors are found to be important (16). Studies on identical twins, and the high prevalence in certain ethnic group have also shown a strong association between genetics, and familial type II diabetes (13,14). MODY syndrome is a type II diabetes that occur at young age, and has been detected to have a clear genetic predisposition with a dominant type of inheritance

(12). Increasing prevalence rates were also observed in populations with high inbreeding practice, thus, providing evidence in support of the genetic role in diabetes. Indians and the Tamil Indian community in South Africa are examples of such communites (14).

1.3.2 Sedentary life – Style

One third of death in the developed countries has been attributed to sedentary lifestyle and lack of physical activity (15). Adopting regimes for special diets with regular physical exercises seems to reduce the observed death rate, which is mainly due to coronary heart disease, diabetes, and cancer of the colon (15).

Obesity especially central adiposity with resulting insulin resistance and hyper-insulinemia are considered to be the major etiological factors in the development of impaired glucose tolerance and type II diabetes (16,17). Physical activity and exercise are significantly associated with lower incidence of diabetes, even in high-risk group (18,19). Such activities are believed to play a major role in maintaining of beta cell function, weight reduction and improvement of the peripheral tissue sensitivity to insulin and hence reduce the risk of type II diabetes (16,19). This protective effect of physical activity has found to be independent of other risk factors such as age, obesity and gender (16).

1.3.3 Nutrition and Obesity

Until now no kind of nutrients is significantly associated with diabetes (13). On the other hand, diets with high fat and low carbohydrate consumption are accused in disease etiology (13). Such diets are associated with obesity and may results in hyper-lipidemia and hyper-isulinaemia and up to 80-90 %of type II diabetes is obese with central abdominal adiposity (12,16). Studies on obese patients using specific dietary instruction seems to decreases the glucose level and reduce the HbA1c as well as body weight which in turn can enhance the sensitivity to insulin in the peripheral tissue (20).

Recent studies have revealed a strong independent association between low vitamin E status and excess risk of diabetes; this is in support of the theory that free radical stress induces type II diabetes (21). Bottle feeding, mainly with cows milk was also found to be as another risk factor for old age diabetes (22).

1.4.4 Environmental Factors

Changes in dietary and lifestyle habits from the transitional to westernized lifestyle have been reported to increase the prevalence and the incidence of diabetes in some third world countries (12,14,23). In rural areas of Africa, the prevalence of type II diabetes in adult population is about 1% compared to 5% in adult

European population (12). Such changes are believed to be associated with dietary habits and a marked change in physical activities in daily life.

Emigrants from developing countries to industrialized ones are exposed to deep change in their lifestyle and a rapid reorientation toward a sedentary lifestyle. Such change has proven to predispose the markedly higher prevalence and incidence of the disease among those emigrants compared to local original population (14,24).

1.3.5 Aging

Prevalence of diabetes seems to increase with age (14,16,23) and studies in some ethnic groups showed that up to 52% of men and 57.7 of woman aged 65-74 years had either impaired glucose tolerance or diabetes (14).

1.4 Lipids and Lipoproteins in Diabetes Mellitus

Diabetes mellitus increases the risk of death and disability due to various disease complications including atherosclerosis, cerebro-vascular disease and / or peripheral vascular disease (25). The lipoproteins, which are considered as risk factors in non-diabetic individuals, occur in diabetic patients (26,27). In general, lipoproteins are anti-atherogenic in individuals with IDDM who have good glycemic control, but in contrast the lipoproteins are

atherogenic in NIDDM subjects regardless the mode of treatment (28).

High concentration of triglycerides and low level of HDL-cholesterol (25,28,29) characterize diabetic dyslipidaema in NIDDM, and these abnormalities are mainly related to abnormal physiology produced by insulin resistance or inadequate insulin action, with concomitant metabolic disturbance (25). Dyslipidaemia are also found in glucose tolerant first-degree relatives of NIDDM patients (28,30). Recent recognition that hypertriglycerdaema is associated with metabolic disturbances of both LDL and HDL-cholesterol, and post-prandial triglycerides rich particles have extended our understanding of metabolic derangement of lipoproteins in diabetes (28,29).

The most common dyslipidaema in NIDDM is related to triglycerides and HDL-cholesterol metabolism (25). NIDDM subjects have higher triglycerides and lower HDL cholesterol than non-diabetic individuals (25,28,29,31,32,33). The low level of HDL-cholesterol in NIDDM is mainly due to high triglycerides level, degree of central or inter-abdominal obesity, glucose and insulin levels (25,28,29). It was found that elevated triglycerides and low HDL-cholesterol are not an isolated metabolic aberrations

but commonly go hand in hand, thus the current hypothesis is that low HDL-cholesterol is due to high triglycerides level (28,29,33).

Total and LDL-cholesterol concentration are similar among NIDDM patients, age and obesity matched non-diabetic ones (25,29). However, it appears to have higher prevalence of small dense LDL cholesterol particles among NIDDM patients, and this small dense LDL cholesterol particles resulted from higher triglycerides levels, and may also have familial genetic component (25, 28, 29, 33, 34). The level of LDL cholesterol is found to be higher in population that consume more saturated fat and cholesterol in their diet (e.g. Americans with NIDDM have higher LDL cholesterol than Japanese NIDDM population). Levels of LDL cholesterol are behind the worldwide geographic variation in the risk of coronary heart disease among NIDDM patients (25,32).

High levels of triglycerides and lowers level of HDL cholesterol were also found in pre-diabetic individuals and this is mainly due to central obesity and higher insulin levels. High blood pressure may also contribute to higher triglycerides and lower HDL-cholesterol levels (28).

1.4.1 Mechanisms of Dyslipidaema in NIDDM

Several mechanisms are believed to be involved for lipid abnormalities in NIDDM patients. These include insulin

suppression of the production of buoyant VLDL particles in the liver of non-diabetic individuals but not in NIDDM ones (29); suppression of the release of free fatty acid from adipose tissue thus, high level of free fatty acid will efflux to the liver and be used for VLDL production (29,35). The catabolism of triglycerides rich particles is initiated by lipoprotein lipase, an enzyme that hydrolysis the triglycerides moiety of chlyomicrons and VLDL, and release fatty acids that is used as energy source in muscles and for storage in adipose tissue. The activity of lipoprotein lipase enzyme is slightly affected in NIDDM individuals, however, a noticeable decrease in the activity of such enzyme is observed among patients with both NIDDM and coronary artery disease (28,29). Enzyme activity is found to be low in untreated or poorly controlled NIDDM and increases with good glycemic control (29,31). In NIDDM, the lipolytic cascade of triglycerides rich lipoproteins is delayed due to shortage of catalytic site on lipoprotein lipase and overproduction of triglycerides saturate the available sites. Thus, both mechanisms are involved in promoting hypertriglyceridaema (29,31).

LDL cholesterol levels in NIDDM are increased because of decreased clearance of LDL cholesterol. The mechanism for impaired removal of LDL cholesterol is due to increase production secondary to VLDL production and decreased clearance (31). Some

individuals with NIDDM, show low levels of LDL cholesterol due to impaired conversion of VLDL to LDL cholesterol. Such patients usually have low or normal LDL cholesterol level but increased level of atherogenic LDL-cholesterol and a low level of HDL-cholesterol due to decreased production and increased catabolism (31).

.4.2 Postprandial Lipaemia

The rise in triglycerides rich lipoprotein after fat containing meal is greater in NIDDM patients than non-diabetic ones (29,33). Postprandial rise of triglycerides rich lipoproteins comprises of both intestinally derived chylomicrons and VLDL of hepatic origin (28). The rise in triglycerides rich lipoproteins is associated with potentially atherogenic alterations of both HDL-cholesterol and LDL-cholesterol particles, which become triglycerides rich and thus, more exposed to hydrolysis by hepatic lipase. The end products being small, dense, HDL and LDL (28,29,33).

Hepatic lipase activity is raised in NIDDM patients (28,31), who exhibit post-prandial elevation of free fatty acid levels compared to non-diabetic ones. The free fatty acids may have deleterious effect on VLDL metabolism (28).

Postprandial lipaemia in NIDDM patients is mainly due to the competition between chylomicron (28), that has been absorbed from

the gut, and VLDL, of hepatic origin. This is mainly due to the fact that chylomicrons are large and with a greater affinity than VLDL particles for lipoprotein lipase (29). The overproduction of VLDL in NIDDM patients saturates the lipolytic capacity (28,29) and accordingly accumulation of VLDL particles will occur as a result of chylomicronaemia and the overproduction of VLDL in the liver in the posprandial state. This usually results in bouts of hypertriglyceridaemia (28). Chylomicrons may not be directly atherogenic but postprandial lipaemia results in atherogenic lipoproteins profile (28).

1.5 Diabetes and Hypertension.

Diabetes and hypertension are two of the most common diseases in westernized; industrialized civilizations and both show increased incidence with age (36, 37). They are interrelated diseases and if untreated, they strongly predispose to cardiovascular and renal diseases. About 2.5–3 million Americans have both diabetes and hypertension where hypertension seems to contribute to 35-75% of cardiovascular morbidity and mortality in diabetic patients. It is the major cause of blindness, cerebral, renal and peripheral atherosclerotic diseases (36,37,38), which is approximately twice as common in diabetic patients as in non-diabetic individual (37).

The prevalence of hypertension in diabetic patients appears to be twice than that in non-diabetic individual (36). The time course and natural history of hypertension varies between type I and type II diabetic patient's (37). In type I patients, hypertension remains normal during the first 5-10 years of diabetes and it develops at the onset of renal disease while in type II diabetes, hypertension is frequent at the time of diagnosis (36,37). The increase in blood pressure is associated with obesity, physical inactivity and the advanced age. These factors are characteristic of people with type II diabetes (35,37).

Hypertension is more prevalent in diabetic men than women less than 50 years of age and more common in women thereafter. Among diabetic subjects in most ethnic and racial groups the prevalence of hypertension increases with age, obesity and the duration of diabetes, particularly if proteinuria is present (36,37).

Both type II diabetes and hypertension share certain risk factors such as obesity, visceral adiposity and possible insulin resistance. The later has been proposed as a link between hypertension and glucose intolerance (35,36,37).

Despite the increasing evidence that hyper-insulinamia may play a role in the genesis and maintenance of hypertension, clearly other factors are also operative. This is supported by the finding of

one third of type II and half of type I diabetes remain free of hypertension despite the presence of insulin resistance and hyper-insulinamia. Thus, the ability of insulin resistance to cause elevated blood pressure may occur in-patients with other genetic risk factors for hypertension (36,37,39).

1.6 Diabetes and Complication

Type II diabetes is a common multi-metabolic disorder leading to high rate of macro and micro-vascular disease (40). NIDDM patients are at greater risk of dying young, particularly of macro-vascular disease. Also morbidity related to micro-vascular is high, but is less than in macro-vascular disease (41,42).

Nine years after diagnosis of NIDDM patient's, 29% of them develop diabetes-related end point and 9% were died (43). In another study, NIDDM patients showed a high prevalence rate of complication of micro-and macro-vascular disease (40).

Retinopathy is strongly related to the duration of diabetes, after 20 years of diabetes, nearly all patients of type I and around 60% of type II diabetes have some degree of retinopathy (44). Where as, about 20-30% of types I and II diabetes develop evidence of nephropathy. In NIDDM patients a considerably smaller fraction

progress to end stage renal disease (45,46,47). Racial and ethnic variability of diabetic nephropathy was also observed (44,45,46).

Data regarding incidence and prevalence rates of neuropathy is not so far available, mainly due to the inconsistency in defining neuropathy. However, a large prospective study on diabetic out patients showed a rise in the prevalence from 7.5% at the time of diagnosis to 50% after 25 years (48), while the prevalence of nephropathy was the least with 12.9% (45).

A considerable racial and ethnic variability in the macro-vascular complication among NIDDM patients was observed. A study among American black and white population showed that 31% and 44% died as a result of coronary heart disease, respectively (41).

The main risk factors that contribute to this complication are, age, duration of diabetes, blood pressure, smoking, dyslipideamia, over-weight, hyperglycemia and others (40,41,42).

1.6.1 The Biochemical Pathogenesis of Diabetic Complication

Diabetic micro-vascular complication results from the interaction of metabolic, genetic and other factors, of which hyperglycemia are most significant. Epidemiological and long term clinical studies suggest that hyperglycemia, or closely associated factors, are of major importance in both the initiation and progression of micro-vascular disease (49).

Hyperglycemia appears to damage tissues by causing both acute, reversible changes in cellular metabolism and cumulative, irreversible alterations in stable macromolecules (45,49)

1.6.1.1 Acute Reversible Metabolic Changes

The acute reversible metabolism results from hyperglycemia include the followings:

1.6.1.1.1 Polyol Production

Hyperglycemia enhance the polyol pathway that result in the increase the metabolism of glucose to sorbitol which is catalyzed by aldose reductase enzyme, which has been suggested as a possible mechanism of microvascular disease in diabetes (45,49,50).

Sorbitol dose not easily diffuses across cell membrane and osmotic damage to cells may occur where accumulation of sorbitol levels is high, such as in the lens during the development of diabetic cataracts. In other tissues such as peripheral nerve, sorbitol levels are too low in diabetes to cause osmotic damage and thus other consequences due to increased polyol pathway flux might take place (49).

1.6.1.1.2 Polyols, Myoinositol and Protein Kinase C

Myoinositol is precursor of phospho-inositides such as phosphotidyl inositol that structurally related to glucose. It is present in most animal and plant tissues, at higher intracellular than

extracellular concentration. One explanation for intracellular myoinositol depletion in diabetes is that glucose competes with myoinositol for cellular uptake, also a link between sorbitol accumulation and lowered myoinositol levels indicates that sorbitol affects myoinositol uptake into the cell (49). New evidence suggests that myoinositol depletion cause neuronal abnormalities by decreasing Na^+K^+ ATPase (49).

Sorbitol–myoinositol derangement has also been implicated in glomerular hyperfiltration, increased permeability of the blood/ retinal barrier and possibly the association of hypertension with diabetes as Na^+K^+ ATPase in vascular smooth muscle may control the contractile response to hormones and neurotransmitters (49). In nerves, protein kinase C activity is reduced and this is associated with decreased Na^+K^+ATPase activity, where as, in vascular tissues, hyperglycemia is associated with an increase in protein kinase C activation. This activation may be involved in abnormal growth and synthesis in the diabetic vasculature (50).

1.6.1.1.3 Early Glycosylation Product

In diabetic individuals, glucose is rapidly attached to amino groups of proteins via the non-enzymatic process of nucleophilic addition to form Schiff's base adducts. This adducts reach equilibrium levels, which are proportional to the blood glucose

concentration, and they undergo the amadori rearrangement to from more stable early glycosylation product (49).

Excessive formation of early glycosylation products may negatively affect a variety of functions that is related to diabetic complication, including the uptake of low-density lipoprotein and the regulation of free radical mediated vascular damage (45,51,52).

The main factors that determine the extent of early glycosylation product *in vivo* are the glucose concentration and the duration of exposure (45,49).

1.6.1.2 Chronic Irreversible Changes in Stable Macromolecules

Some early glycosylation products dissociate, but those formed on collagen, DNA and other long lived macromolecules slowly undergo further complex chemical rearrangement, which are irreversible, to form advanced glycosylation end products (AGE) (49). Glucose–derived advanced glycosylation products apparently result from covalent cross-linking of protein molecules. The formation of advanced glycosylation products could contribute to the development of diabetic tissue damage in several ways (45,49).

1.6.1.1 Cross-Linking of Extracellular - Matrix Proteins.

In vitro, human LDL binds covalently to collagen modified by advanced glycosylation in direct proportion to the content of AGE, indicating that LDL binds specifically to AGE (53). This finding

suggests that excessive cross–linking by hyperglycemia -induced AGE may accelerate atherosclerosis in diabetic patients, even at normal LDL-cholesterol level (49). In the diabetic microcirculation, PAS-positive material is deposited in retinal, glomerular and endoneurial arterioles together with plasma proteins such as IgG, albumin, and IgM, which accumulate in the basement membrane. Once the proteins bind to the matrix components, it cannot be extracted even with high-salt buffer or thiocyanate treatment (49). Once these proteins such as LDL-cholesterol and IgG become covalently attached to vascular matrix AGE, further AGE form on these proteins and serves as attachment site for additional molecules of extravasated plasma proteins. Also AGE on matrix proteins can cross-link adjacent matrix components such as collagen, forming covalent and heat stable bonds throughout the collagen molecule. This matrix component cross linked by glucose accumulates in diabetic vessel wall, because they are less susceptible to normal enzymatic degradation. All of these processes will result in luminal narrowing of both small and large vessels and could result in tissue injury from AGE-catalyzed oxygen radical formation (45,49).

1.7 Diabetes Epidemiology

Diabetes is considered as a growing and life-threatening health problem for the whole world (54). A massive increase in the global prevalence of diabetes is likely to occur as "Westernization" of dietary habits and patterns of physical activity, which becomes more widespread (23,55). The number of people that affected by diabetes is suspected to increase, and by the year 2020, the number of diabetes will be around 250 millions (55).

The higher incidence is expected to occur in developing countries adopting rapid westernized way of life (12). The prevalence of the disease varies considerably between population. This variability has been attributed to differences in genetic susceptibility, population age structure, degree of socio-economic development, diet, level of risk factors and variability in study methodology (14). Wide spread of similar diagnostic criteria recommended by WHO and the National Diabetes Data Group (NDDG) over the last decade has allowed the prevalence of the disease to be easily estimated and compared (14).

The variation in the prevalence could range from 3-50% between communities (12, 56). The prevalence of diabetes has been estimated to be 6-7% for peoples aged 45-64 years, and 10-12% for 65 years and above (43).

1.8 Diabetes Epidemiology in the Arab Countries

Several studies have been conducted in several Arab countries in order to estimate the prevalence of diabetes. The prevalence rate of 13.4%, 14.8%. 13.1% and 10% were reported in Jordan, Kuwait, Oman, and Tunisia, respectively (56,57,58). Risk factors that contribute to such high prevalence rates were, overweight, physical inactivity and family history (56,57,58).

1.9 Diabetes in Palestine

Studies enlightening the epidemiology of diabetes in the Palestinian community are scarce. Data about the Prevalence are extracted from the registries of health services in governmental and UNRWA diabetes clinics. Patients attending private sector or people with undiagnosed diabetes are therefore underrepresented in any estimation of the incidence of diabetes (59). In 1995 the Community Health Department, Birzeit University conducted a study that showed an increased role of diabetes in morbidity and mortality rates (60). The same study, based on amputations surgical reports from Al-Ahli-Hospital at Hebron, showed that diabetes complication were behind most of these operations and around 48% of patients admitted to the medical department were diabetic or with diabetic complication (60).

A study on the prevalence of diabetes in Palestine is conducting by AL-Quads university in which the primarily result show that the prevalence rate is around 9.1% (61).

The risk factors that contribute to the occurrence of diabetes in Palestine are not known, however, genetic, environmental and lifestyle factors are expected to be involved (58,62).

1.10 Socio – Economic Impact of Diabetes

Diabetes is a major health problem and the leading cause of death (63). It is the most common cause of blindness among middle age and elderly people and a major cause of renal failure resulting in further need for dialysis and or kidney transplants (55). It is the most common cause of lower limb amputation. In addition diabetes increases the risk for myocardial infarction or stroke, and which may lead to functional disability (55,63).

By year 2020 the number of diabetic patient is expected to exceed 250 millions (55). Apart from the human suffering, this epidemic will undoubtedly limit the funds available for the treatment and prevention of other diseases in poor countries (55).

More than 13 million people are estimated to have diabetes in U.S.A (64). Nearly half of them don't know if they have the disease and therefore are not receiving treatment while silent damage may

place them at greater risk for heart attack, strokes, Kidney failure, blindness and amputations (65). This complication may result in low self-esteem and even clinical depression (55).

In 1992, diabetes costs American Authority around 92 billion dollar, 45.2 billion in direct medical cost and 46.6 billion in lost of productivity due to disability and premature death (65,66). In Israel, the prevalence of diabetes is 3.5% in women, and 4.3 in men and this rate increases to 10.3% at the age of 60years or more (67). A study to estimated cost of hospitalization for diabetic patients in eight hospitals was found to be 36 million dollar, which constitutes around 10.2% of the total budget of these hospitals (68). From all of the above mentioned, it is clear that diabetes is a growing serious public health problem that requires a great attention in all countries.

1.11 Aims of the Study.

Since no pervious studies were conducted regarding the clinical status of NIDDM patients in Palestine, the current study aimed at: First evaluating the clinical status; Secondly, trying to pin point any underlying risk factors in our community. Such preliminary data will be of great value in adopting any future strategies regarding the treatment and prevention of this disease.

Chapter II

Materials and Methods

2.1 Background

Nablus is considered as the third largest district in the number of population after Hebron and Ramallah, with a population of 251 thousands. The community in Nablus as well as in other districts is distributed into three main demographic groups with specific socio-economic characteristics. These groups live in the city, refugee camps, and villages. Health services in Palestine are offered by four different health care providers, the Palestinian National Authority (Ministry of health), UNRWA health program, NGOs, and the private sector.

Special programs for treating diabetic patients are offered by; governmental diabetic clinics in the primary health care department, UNRWA diabetic clinics in refugee camps, modest number of NGO's clinics and private sector.

A governmental diabetes clinic of the primary health care in the City Nablus and two diabetes clinics in Balata and En-Beatelma'a refugee camps run by UNRWA health department were selected for conducting the present study.

The governmental diabetic clinic in Nablus offers its services to about 2000 diabetic patients from both the city as well as the whole district, while the UNRWA clinics provides its services to about 1000 diabetic patients of the three refugee camps.

Permissions to conduct the study in the clinics were obtained from the Ministry of Health and the UNRWA main office in Jerusalem.

2.2 Sample selection

The study focus was on the NIDDM patients receiving health care in the selected clinics. The treating physicians made classification of the cases according to the types of diabetes.

From September 1998 to May 1999, a total of 323 NIDDM patients were selected in a systematic and random way; 215 NIDDM patients were from Nablus governmental diabetes clinic and 108 NIDDM patients were from UNRWA clinics. This sample represents around 10% of the total NIDDM patients in these clinics.

A small non-Diabetic sample (49 cases) was systematically selected from the general population. Each participant signed a written consent.

2.3 **Data selection**

A questionnaire was developed for the study aiming to obtain demographic and physical data such as gender, age, profession, and marital status. Age parameter was categorized into three groups of age, 35-50, 51-60, and above 60 years. Participants were interviewed and staff nurse in the clinics filled the questionnaires.

Data on the occurrence and the degree of complication (retinopathy, nephropathy, neuropathy, and cardiovascular disease) were obtained from patient's medical files. Smoking habit was obtained by patients self reporting and was classified as smoker, ex-smoker, non-smoker.

2.4 Anthropometric and Blood Pressure Measurement

Body height was measured to the nearest 0.5cm. Body weight was measured to the nearest 0.1kg. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Blood pressure was measured according to standard protocols.

2.5 Biochemical Analysis

Blood samples were collected in plain or EDTA tubes after an overnight fasting. The blood was left at room temperature for 15 minutes until complete clotting, then the serum was harvested by centrifugation at 4000 rpm for 5 minute.

Sera samples were analyzed within 2 hours of preparation. In some cases samples were stored at 2-8°C for 4 days or at -20°C for 2 weeks until tests were performed (69). Samples were analyzed for glucose, cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Glucose (70), cholesterol (71), triglyceriedes (72), were assayed by standard enzymatic methods (BioMeriex Sa France) using Shimadzu UV 1201 V spectrophotometer. HDL and LDL levels were determined using standard enzymatic methods after precipitation with $Mgcl_2$/phosphotungstic acid (73) and polyanion5sulfate (74), respectively, by the same spectrophotometer, using BioMeriex Sa France kindly donated by AL- Walid Medical Trading Co. One level of quality control was performed with each run with CV less than 6.5%, 4%, 4.5%, 4% and 3% for triglycerides, cholesterol, HDL-c, LDL-c and glucose respectively. Fresh morning urine samples were obtained and tested for proteinuria using selfstick technique.

2.6 Data Analysis

Statistical Package for Social Science (SPSS) was used to analyze the collected data. The calculate values included:

1. Means, standard errors, and frequencies.
2. Independent T-test.
3. One-way analysis of variance (ANOVA) and variation significance was determined using (LSD) post-hoc test.

3.1 General Characteristics of the Study Groups

3.1.1 Demographic Information

The age range of the study participants in NIDDM population was from 35 to 73 years with mean age of 56.5 ± 0.5. In non-diabetic population, age ranged from 35 to 71 years with mean age of 54.4± 1.5. Table (1) describes the general demographic information of the study participants.

Table 1- Demographic Information According to Age

	35- 50 years (92)		51- 60 years (116)		> 60 years (164)	
	NIDDM (68) No (%)	Non– Diabetic (24) No (%)	NIDDM (106) No (%)	Non- Diabetic (10) No (%)	NIDDM (149) No (%)	Non- Diabetic (15) No (%)
Sex						
Male	32 (47)	10(41.5)	32(30)	1(10)	68(45.6)	5(33)
Female	36 (53)	14(58.5)	74(70)	9(90)	81(54.4)	10(67)
Marital Status						
Married	66 (97)	23(96)	101(95.3)	10(100)	147(98.7)	13(86.7)
Single	2 (3)	1(4)	5(4.7)	------	2(1.3)	2(13.3)
Place of Residency						
City	19(28)	11(46)	25(23.5)	3(30)	64(42.9)	9(60)
Village	32(47)	10(41.5)	55(51.9)	6(60)	72(48.3)	5(33.3)
Refugee Camps	17(25)	3(12.5)	26(24.6)	1(10)	13(8.8)	1(6.7)
Class of Profession						
Office employees	13(19)	9(37.5)	5(4.7)	2(20)	3(2)	------
Outdoor labor	18(27)	2(8.5)	13(12.3)	-----	20(13.4)	2(13.3)
House keepers	34(50)	11(45.5)	67(63.2)	7(70)	72(48.3)	9(60)
Unemployed	3(5)	2(8.50	21(29.5)	1(10)	53(36.3)	4(26.7)

Women were represented with a higher proportion among the participants, both NIDDM and Non-diabetic, three age groups compared to men. The difference was greatest among age group 50-60. The majority of participants in NIDDM and non-diabetics were married.

3.1.2 General Characteristics

The general characteristics of both NIDDM and non-diabetic populations are shown in table (2).

Table 2- Characteristics of NIDDM and Non-diabetic Population

	Non-Diabetic (49)	NIDDM (323)
Age (years)	54.4± 1.5	56.5 ± 0.5
Height (cm)	161.6 ± 1.4	160.8 ± 0.5
Weight (kg)	80.8 ± 2.4	79.0 ± 0.8
BMI (kgm2)	30.8 ± 0.7	30.6 ± 0.3
BP – Syst (mm Hg)	127.6 ± 2.0	137.6 ± 1.1*
BP – Dias (mm Hg)	84.3 ± 1.1	83.3 ± 0.5
BFG (mg %)	86.5 ± 2.1	183.3 ± 3.7*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetics at p< 0.001.*

The mean age for the NIDDM (56.5 ± 0.5 years) showed no significant difference from the mean of 54.4 ± 1.5 years for non-diabetic population. Mean systolic blood pressure is significantly higher in NIDDM than in non-diabetic population.

Several studies showed that diabetes and hypertension are common diseases that coexist at greater frequency than chance alone would predict (36,37). It was also reported that up to 28% of

NIDDM hypertensive observed at the time of diagnosis (36), and the prevalence of hypertension in diabetic patients is approximately twice that in the non-diabetic population (37).

The American Diabetic Association and other studies showed that the time course and the natural history of hypertension differ markedly between IDDM patients and those of NIDDM. In IDDM patients the hypertension is characterized by elevation of systolic and diastolic blood pressures. In contrast to type I diabetic patients, hypertension in type II diabetes is characterized by elevation of isolated systolic blood pressure (33,36,37). Other studies also showed that hypertension in NIDDM patients is characterized by high level of systolic blood pressure with normal or slightly increased diastolic pressure (33,42,75).

3.2 Body Mass Index and Obesity

Table 2 shows the mean BMI as calculated from measured height and weight. BMI mean value of non-diabetic population (30.8 ± 0.7) was similar to that of NIDDM (30 .6 ± 0.3). The BMI values in both populations fall in the obese range (defined as having a BMI > 30.0).

Table 3 shows the distribution of obesity of both NIDDM and non-Diabetic population. Data in table 3 showed that up to 56.6% and 52.9% of the non-diabetic and NIDDM population are obese,

respectively. Combining obese and overweight ranges (having a BMI >27.0), as shown in table 2, 78.6% of the non-diabetic population are overweight compared to 73.7% in the NIDDM population.

Table 3 - Prevalence of Obesity

BMI	Obesity	Non-Diabetic		NIDDM	
>24	Lean	12-2	21.4*	7.7	26.3*
24-27	Normal	9.2		18.6	
27-30	Overweight	20.5	78.6 +	20.8	73.7 +
≥30	Obese	56.6		52.9	

* Designates a combination of *lean* and *normal* BMI values.
\+ Designates a combination of *overweight* and *obese* BMI values.

Tables 4 and 5 show the general characteristics and lipids profile in NIDDM and non-diabetic populations with BMI below and above the average value 25 kg/m2.

Table 4 shows the effect of BMI factor on the characteristics of NIDDM and non-diabetic populations. NIDDM patients with BMI>25 showed a significant increased in both systolic and diastolic blood pressure compared to NIDDM patients who showed BMI <25.

Table 4 - Characteristics of NIDDM and Non–diabetic populations with increasing BMI.

	Non-Diabetic (49)	NIDDM (321)
Age		
BMI > 25	55.0 ± 1.6 (43)	56.5 ± 0.5 (278)
BMI < 25	49.8 ± 2.6 (6)	56.8 ± 1.5 (43)*
Height (cm)		
BMI > 25	161.2 ±1.5	160.3 ± 0.5
BMI < 25	164.2 ± 3.3	164.1 ± 1.4
Weight (kg)		
BMI > 25	83.9 ± 2.3	81.4 ± 0.8
BMI < 25	58.3 ±3.5^{+}	63.0 ± 1.3^{+}
BP – Syst (mmHg)		
BMI > 25	129.5 ± 2.1	138.6 ± 1.1*
BMI < 25	113.3 ±3.3^{+}	131.2 ± 2.6*$^{+}$
BP – Dias (mmHg)		
BMI > 25	85.6 ± 1.1	83.9 ± 0.6
BMI < 25	75.0 ± 2.2^{+}	79.4 ± 1.3^{+}
BFG (mg%)		
BMI > 25	87.2 ± 2.1	181.3 ± 4.0*
BMI < 25	77.0 ± 5.0	193.4 ± 10.0*

Data are means ± SE for the number of cases appears in parenthesis.
* *Denotes significance from Non-Diabetics at p< 0.05.*
$^{+}$ *Denotes significance from group with BMI>25 values at p<0.05*

Non-Diabetic individuals with BMI<25 was younger than those with BMI>25. In addition lower BMI (<25) reduced significantly the mean values of systolic and diastolic blood pressure.

Several studies showed that systolic and diastolic pressure are higher in both diabetic and non-diabetic individual with a higher BMI compared to lean individuals (36,37,75,76).

Franklin and coworkers showed that insulin-resistant and hyper-insulinemia is more severe and closely associated with hypertension in obese patients compared to lean individual (39).

Table (5) shows the distribution of plasma lipids and lipoproteins in both NIDDM and non- diabetic populations with BMI below and above 25 kg/m2.

As shown in table (5), mean levels of total cholesterol, LDL cholesterol and triglycerides in NIDDM with BMI >25 are higher compared with BMI < 25 in the same population. Such differences were of no statistical values, with the exception of triglycerides. HDL cholesterol didn't show any significant differences.

In non-diabetic population both total and LDL cholesterol were significantly higher in individuals with BMI >25 compared to those with BMI < 25. Mean triglycerides levels in non-diabetic populations were higher in individuals with BMI >25 compared to those with BMI < 25 but, such differences were of no significant values. HDL cholesterol didn't show any significant differences.

Table 5 – Plasma lipids and lipoproteins level in NIDDM and Non–diabetic populations with increasing BMI.

	Non-Diabetic (49)	NIDDM (321)
Cholesterol		
BMI > 25	211.2 ± 5.4 (43)	221.2 ± 2.7 (278)
BMI < 25	175.0 ± 12.3 (6)$^{+}$	216.7 ± 8.2 (43)*
HDL- Cholesterol		
BMI > 25	44.9 ± 1.6	39.3 ± 0.7*
BMI < 25	42.1 ±3.4	38.5 ± 1.2
Cholesterol/ HDL-Cholesterol	4.9 ± 0.2	5.9 ± 0.1*
BMI > 25	4.2 ± 0.2^{+}	5.8 ± 0.3*
BMI < 25		
LDL- Cholesterol		
BMI > 25	135.2 ± 4.7	135.2 ± 2.2
BMI < 25	103.7 ±10.8*$^{+}$	131.3 ± 6.3*
Triglycerides		
BMI > 25	129.3 ±11.9	170.9 ± 6.5*
BMI < 25	83.8 ± 7.25	140.4 ± 12.2*$^{+}$

Data are means ± SE for the number of cases appears in parenthesis.
* *Denotes significance from Non-Diabetics at p< 0.05.*
$^{+}$ *Denotes significance from group with BMI>25 values at p<0.05*

Cholesterol, triglycerides and cholesterol/HDL in NIDDM patients with BMI more or less than 25Kg/m^2 are significantly higher compared to that of non-diabetic subjects. However, cholesterol levels in NIDDM patients with BMI>25 are higher than that observed among non-diabetic individuals. Such differences were of no statistical differences.

HDL-cholesterol in NIDDM patients with 25>BMI>25 is lower compared to non-diabetic subject but, it is only significant between NIDDM patients and non-diabetic individuals with BMI>25.

LDL-cholesterol is significantly higher in diabetic patients with BMI>25 compared to non-diabetic subject.

Several studies showed that increase in BMI is positively associated with hypertension, increased in blood triglycerides, cholesterol, LDL-cholesterol, and decreased in HDL-cholesterol (77,78). A study conducted by Kang *et al* in 1996 showed that obese NIDDM patients had higher blood cholesterol and triglycrides levels compared to obese non- diabetic individual (18). American Diabetes Association and Chaturevdi *et al.* showed that a low degree of central obesity result in a reduction of a therogenic lipids profile (24,42).

Hypertriglyceridemia is known to be highly prevalent in the untreated diabetic patients, usually accompanied by a decrease in high-density lipoprotein (HDL-cholesterol). Table 6 shows the concentration of plasma lipids and lipoproteins in NIDDM compared to non-diabetic population. The presented data show a significant increase in blood cholesterol and triglycerides levels and a decrease in HDL-cholesterol in NIDDM compared to non-diabetic population.

Table 6- Plasma lipids and lipoprotein levels in NIDDM and Non-Diabetic population

	Non-Diabetic (49)	NIDDM (323)
Cholesterol (mg/dl)	206.8 ± 5.3	220.5 ± 2.6*
HDL- Cholesterol (mg/dl)	44.6 ± 1.5	39.2 ± 0.6*
Cholesterol / HDL	4.8 ± 0.2	5.9 ± 0.1*
LDL- Cholesterol (mg/dl)	131.3 ± 4.5	134.6 ± 2.1
Triglycerides (mg/dl)	123.7 ± 10.7	166.8 ± 5.9*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at p<0.02.*

LDL-Cholesterol in NIDDM didn't differ from that observed in non-diabetic population. The higher levels of cholesterol and triglycerides and the low levels of HDL-cholesterol are consistent with reports on different populations (18,25,28,29,31,32,33,75,79). Total and LDL-cholesterol level usually have a similar or slightly higher in NIDDM patients compared to non-diabetic population (18,25,28,29,31,32,33,75,79). Blood lipid concentrations in diabetes have been the subject of a great number of publications. The data presented in table 6 are consistent with the published data concerning the effect of diabetes on serum lipids and lipoprotein levels compared with healthy non-diabetic population as shown in table 7.

Table 7 - Effect of diabetes in serum lipid and lipoprotein levels compared with healthy control population

	NIDDM	*IDDM*
Triglycerides	⇧	⇧ Or N
Cholesterol	⇧ Or N	N or ⇩
LDL	⇧ Or N	N or ⇩
HDL	N or ⇩	⇧ Or N

Source: lipids text, Q.J.Med.70; 1989: 265-276.
Abbreviations:
NIDDM – Non-Insulin Dependent Diabetes Mellitus
IDDM - Insulin Dependent Diabetes Mellitus
VLDL – Very Low Density Lipoproteins
LDL - Low Density Lipoproteins
HDL - High Density Lipoproteins
N – Within the normal range

3.3 Gender differences

The effect of gender differences on the general characteristics and lipids profile in both NIDDM and non-diabetic populations are shown in tables (8 and 9).

Data in table (8) showed that mean body mass index (BMI) and fasting blood glucose (FBG) were significantly higher in women compared to men in NIDDM population, while in non-diabetic population the increased in BMI in women compared to men is not significant.

Table 8 Characteristics of both men and women in NIDDM and Non-Diabetic populations

	Non-Diabetic (49)	NIDDM (322)
Age (years)		
Both sexes	54.4±1.5 (49)	56.5± 0.5 (322)
Men	52.9±2.9 (16)	56.6± 0.8 (131)
Women	55.1±1.7 (33)	56.5±0.6 (191)
Height (cm)		
Both sexes	161.6 ±1.4	160.8 ± 0.5
Men	169.9 ± 2.3	167.6 ± 0.6
Women	157.5 ± 1.3	156.1 ± 0.4
Weight (kg)		
Both sexes	80.8 ± 2.4	79.0 ± 0.8
Men	85.6 ± 4.5	80.0 ± 1.3
Women	78.4 ± 2.7	78.2 ± 1.1
BMI (kgm2)		
Both sexes	30.8 ± 0.7	30.6 ± 0.3
Men	29.5 ± 1.1	28.5 ± 0.4
Women	31.5 ± 0.9	32.1 ± 0.4^{+}
BP – Syst (mmHg)		
Both sexes	127.6 ± 2.0	137.6 ± 1.0*
Men	128.1 ± 4.5	137.7 ± 1.7*
Women	127.3 ± 2.1	137.6 ± 1.3*
BP – Dias (mmHg)		
Both sexes	84.3 ± 1.1	83.3 ± 0.5
Men	84.3 ± 2.2	83.8± 0.8
Women	84.2 ± 1.3	83.0 ± 0.6
BFG (mg%)		
Both sexes	86.5± 2.1	183.8 ± 4.1*
Men	88.3± 4.5	169.1 ± 5.2*
Women	84.7± 1.9	193.4 ± 5.1*$^{+}$

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from Men values at $p<0.05$

Table (8) also shows that systolic blood pressure is significantly higher in both diabetic men and women compared to the non-diabetic population. Both systolic and diastolic blood pressures did not show any differences between women and men in both populations.

Table 9 shows the distribution of blood lipids and lipoproteins in both men and women in NIDDM and non-diabetic populations. Both triglycerides and cholesterol were significantly higher in NIDDM men and women compared to non-diabetic population.

Table 9 - Plasma lipids and lipoproteins levels in both diabetic men and women compared with healthy control population

	Non-Diabetic (49)	NIDDM (323)
Cholesterol (mg/dl)		
Both sexes	206.8 ± 5.3 (49)	220.5 ± 2.6 (322)*
Men	196.0 ± 9.0 (16)	220.3 ± 4.0 (131)*
Women	212.0 ± 6.4 (33)	220.7 ± 3.4 (191)
HDL- Cholesterol (mg/dl)		
Both sexes	44.6 ± 1.5	39.2 ± 0.6*
Men	39.2 ± 2.3	37.3 ± 0.8
Women	47.2 ± 1.8^{+}	40.5 ± 0.9*$^{+}$
Cholesterol / HDL		
Both sexes	4.8 ± 0.2	5.9 ± 0.1*
Men	5.2 ± 0.3	6.2 ± 0.1*
Women	4.7 ± 0.2^{+}	5.8 ± 0.1*$^{+}$
LDL- Cholesterol (mg/dl)	131.3 ± 4.5	134.6 ± 2.1
Both sexes	130.6 ± 8.1	134.8 ± 3.3
Men	131.7 ± 5.6	134.4 ± 2.6
Women		
Triglycerides (mg/dl)		
Both sexes	123.7 ± 10.7	166.8 ± 5.9*
Men	123.3 ± 13.7	168.6 ± 9.4*
Women	112.9 ± 9.3	165.5 ± 7.6*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.02$*
$^{+}$ Denotes significance from Men values at $p<0.05$

Differences in total cholesterol, LDL-Cholesterol and triglycerides levels in both genders of NIDDM and non-diabetic

populations were insignificant while, HDL-Cholesterol levels were significantly higher in women than in men in both populations.

3. 4 Effect of Cigarette Smoking

The effect of cigarettes smoking on the general characteristics and lipids profile is shown in tables (10 and 11). The data presented in table (10) shows that systolic pressure in non-diabetic population was the only affected parameter. Diabetic status didn't show additional increase in systolic pressure beyond that caused by smoking cigarettes.

Table 10 – Effect of smoking cigarettes on the characteristics of NIDDM and Non-Diabetic Populations

	Non-Diabetic (45)	NIDDM (294)
Age		
Smokers	53.9 ± 3.5 (12)	57.4 ± 11.0 (59)
Non-smokers	53.7±1.7 (33)	59.4 ± 9.4 (235)
Height (cm)		
Smokers	162.4 ± 2	163.9 ± 1.2
Non-smokers	162.3 ± 2	159.6 ± 0.5
Weight (kg)		
Smokers	79.3 ± 3.1	81.4 ± 1.9
Non-smokers	81.7 ± 3.3	78.3 ± 1.0
BMI		
Smokers	30.2 ± 1.3	30.4 ± 0.7
Non-smokers	30.6 ± 1.0	30.8 ± 0.3
BP – Syst (mmHg)		
Smokers	132.5 ± 2.8	135.6 ± 2.4
Non-smokers	124.6 ± 2.6^{+}	138.3 ± 1.2*
BP – Dias (mmHg)		
Smokers	86.7 ± 1.9	83.1 ± 1.4
Non-smokers	83.3 ± 1.5	83.5 ± 0.6
BFG (mg%)		
Smokers	81.6 ± 2.7	189.5 ± 9.3*
Non-smokers	87.5 ± 2.7	181.4 ± 4.3*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from smokers values at $p<0.05$

Table 11 – Effect of smoking cigarettes on plasma lipids and lipoprotein levels of NIDDM and Non-Diabetic Populations

	Non-Diabetic (45)	NIDDM (294)
Cholesterol		
Smokers	199.9 ± 12.5 (12)	224.3 ± 5.8 (59)
Non-smokers	209.9 ± 6.1 (33)	219.7 ± 3.1 (235)
HDL- Cholesterol		
Smokers	37.3 ± 1.2	37.3 ± 1.1
Non-smokers	47.1 ± 1.9^{+}	39.9 ± 0.8*
Cholesterol/ HDL-Cholesterol	5.4 ± 0.4	6.3 ± 0.2*
Smokers	4.6 ± 0.2^{+}	5.8 ± 0.1*$^{+}$
Non-smokers		
LDL- Cholesterol	133.5 ± 10.9	134.4 ± 4.5
Smokers	131.8 ± 5.4	134.6 ± 2.5
Non-smokers		
Triglycerides		
Smokers	125.3 ± 10.6	187.5 ± 16.6*
Non-smokers	122.9 ± 14.4	164.3 ± 10.9*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from smokers values at $p<0.05$

Data in table (11) shows that smoking significantly decreases HDL-Cholesterol in non-diabetic population to the same levels observed among NIDDM population. Triglyceride levels were also slightly increased.

3.5 Effect of Increasing Age

The effect of increasing age on the general characteristics and lipids profile is shown in tables (12 and 13).

Table (12) shows the effect of age on the general characteristics of NIDDM patients and non-diabetic population.

Table 12 - Effect of Increasing Age on the Characteristics of NIDDM and Non-Diabetic Populations

	Non-Diabetic (49)	NIDDM (323)
Height (cm)		
35-50 years	165.7 ± 2.0 (24)	163.3 ± 1.1 (68)
51-60 years	161.1 ± 1.1 (9)	160.2 ± 0.8 (106)
> 60 years	155.6 ± 2.4 (16)$^{+}$	160.0 ± 0.7 (149)
Weight (kg)		
35-50 years	84.9 ± 4.0	82.2 ± 1.7
51-60 years	81.6 ± 4.3	81.1 ± 1.5
> 60 years	74.1 ± 3.0^{+}	75.9 ± 1.1
BMI (kgm2)		
35-50 years	30.9 ± 1.3	31.0 ± 0.7
51-60 years	31.1 ± 1.3	31.6 ± 0.5
> 61 years	30.6 ± 1.0	29.8 ± 0.5^{+}
BP – Syst (mmHg)		
35-50 years	121.3 ± 2.0	129.0 ± 1.7^{+}*
51-60 years	126.7 ± 5.0	137.4 ± 1.9*
> 61 years	137.5 ± 3.5^{+}	141.7 ± 1.6
BP – Dias (mmHg)		
35-50 years	82.5 ± 1.5	80.4 ± 1.0
51-60 years	84.4 ±2.4	83.1 ± 0.9
> 61 years	86.9 ± 2.1	84.8 ± 0.8^{+}
BFG (mg%)		
35-50 years	87.6 ± 3.4	187.1± 7.8*
51-60 years	86.7± 2.5	189.2 ± 6.6*
> 61 years	82.9± 2.5	177.3 ±5.5*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from 35-50 years old group values at $p<0.05$

Data presented in this table show that systolic blood pressure is increased with age but the differences were significant only between

age group (35-50) and other age groups. Diastolic pressure also showed a significant increase between the 35-50 years age group and the >61 years age group in diabetic group only.

They were no significant differences in the BMI between the first age group and the second age group. In contrast the BMI is significantly higher in the second age group compared with the third group.

Comparison between diabetic and non-diabetic subjects within the same age groups showed that both BMI and diastolic blood pressure did not show any significant differences. On the other hand, systolic blood pressure was higher in the diabetic group compared to non-diabetic group, and the differences were significant in the first two age groups.

Increased level of systolic and diastolic pressures in our study is consistent with previous studies (32, 36, 39). Other studies showed that BMI was positively associated with age (80), but negatively associated with the duration of diabetes (75). In 1996, Al-sha'ar *et al* reported a slight decrease BMI with increasing age in diabetic patients with a long disease duration (59).

Table 13 - Effect of Increasing Age on the Plasma lipids and lipoprotein levels of NIDDM and Non-Diabetic Populations

	Non-Diabetic (49)	NIDDM (323)
Cholesterol		
35-50 years	195.6 ± 6.6 (24)	222.4 ± 5.7 (68)*
51-60 years	212.6 ± 14.2 (9)	220.0 ± 4.4 (106)
> 61 years	220.2 ± 9.1 (16)+	220.0 ± 3.8 (149)
Cholesterol/ HDL		
35-50 years	4.9 ± 0.2	5.9 ± 0.2*
51-60 years	4.6 ± 0.5	6.0 ± 0.2*
> 61 years	4.8 ± 0.3	6.0 ± 0.1*
HDL-Cholesterol		
35-50 years	40.7 ± 1.5	39.6 ± 1.0
51-60 years	47.8 ± 3.5	38.5 ± 0.9*
> 61 years	48.5 ± 3.2+	39.6 ± 1.0*
LDL- Cholesterol		
35-50 years	126.5 ± 5.9	130.6 ± 4.1
51-60 years	132.2 ±12.2	136.7 ± 3.5
> 61 years	138.2 ± 8.4	134.9 ± 3.2
Triglycerides		
35-50 years	139.3 ± 19	181.4 ± 16.9
51-60 years	110.0 ± 24.1	170.6 ± 10.6*
> 61 years	108.1 ± 7.9	157.4 ± 6.8*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
+ Denotes significance from 35-50 years old group values at $p<0.05$

Table (13) shows blood lipids profile in both NIDDM and non-diabetic populations among the various age groups.

Data presented in this table shows that LDL-cholesterol levels were increased with age in all age groups among both diabetic and non-diabetic populations. Among non-diabetic subjects, total and HDL-cholesterol showed a significant increase in their levels. However, diabetic population showed similar elevated cholesterol levels among all age groups. This level was statistically significant when compared all age group with the age group 35-50 years of non-

diabetic subjects. HDL-cholesterol levels showed no differences among NIDDM age groups and was significantly lower in the 51-60, and >61 age groups compared to non-diabetic subjects.

Triglycerides levels showed a slight decrease with age among all studied age groups in both diabetic and non-diabetic subjects.

3.6 Place of Residence

Data presented in tables (14 and 15) show general characteristics and lipids profile in NIDDM and non-diabetic populations according to place of residence.

Table 14 - Characteristics of both NIDDM and Non-diabetic populations according to place of residence.

	Non-Diabetic (49)	NIDDM (322)
Age		
City	55.3 ± 2.4 (24)	57.4±0.9 (106)
Village	53.2 ± 2.0 (20)	56.8 ± 0.6 (160)
Refugee's Camp	54.8 ± 3.8 (5)	54.2 ± 1 (56)
Height (cm)		
City	160.4 ± 1.9	160.7 ± 0.8
Village	162.9 ± 2.6	161.2 ± 0.7
Refugee's Camp	162.0 ± 2.6	159.7 ± 1.1
Weight (kg)		
City	80.2 ± 3.0	78.6 ± 1.4
Village	80.9 ± 4.2	77.3 ± 1.1
Refugee's Camp	83.0 ± 8.0	84.3 ± 1.9
BMI (kgm2)		
City	31.1 ± 1.0	30.6 ± 0.6
Village	30.3 ± 1.2	29.8 ± 0.4
Refugee's Camp	31.6 ± 2.8	33.2 ± 0.8^{+}
BP – Syst (mmHg)		
City	130.0 ± 3.1	139.7 ± 1.9*
Village	125.0 ± 3.0	134.8 ± 1.4*$^{+}$
Refugee's Camp	126.0 ± 5.1	141.8 ± 2.7*o
BP – Dias (mmHg)		
City	85.0 ±1.6	84.3 ± 1.0
Village	83.0 ± 1.9	82.1 ± 0.7
Refugee's Camp	86.0 ± 2.5	84.8 ± 1.4
BFG (mg%)		
City	85.5 ± 3.5	177.6 ± 6.0*
Village	86.7 ± 2.0	189.9 ± 5.6*
Refugee's Camp	84.4 ± 5.9	176.1 ± 8.2*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at p<0.05*
$^{+}$ Denotes significance from city values at p<0.05.
o Denotes significance from village values at p<0.05

BMI was significantly higher among NIDDM refugee's camp inhabitance compared to those from either city or village.

Systolic blood pressure was significantly lower among NIDDM village inhabitance compared to those residing in city or refugee camps. No significant differences were observed among non-diabetic group with respect to BMI, systolic and diastolic pressures in all residential areas.

Table 15 - Plasma lipids and lipoprotein levels in both NIDDM and Non-diabetic populations according to place of residence.

	Non-Diabetic (49)	NIDDM (322)
Cholesterol		
City	211.4 ± 7.2 (24)	224.6 ± 4.3 (106)
Village	202.7 ± 9.2 (20)	224.7 ± 3.8 (160)*
Refugee's Camp	200.8 ± 12.2 (5)	200.9 ± 4.9 (56)$^{+}$
HDL-cholesterol		
City	42.4 ± 2.1	39.4 ± 0.9
Village	45.7 ±2.6	39.1 ± 0.8*
Refugee's Camp	50.6 ± 4.6^{+}	39.2 ± 2.2*
Cholesterol/ HDL		
City	5.2 ± 0.3	5.9 ± 0.1*
Village	4.6 ± 0.2	6.0 ± 0.1*
Refugee's Camp	4.0 ± 0.3^{+}	5.7 ±0.2*
LDL-cholesterol		
City	138.2 ± 6.0	135.9 ± 3.3
Village	124.8 ± 8.1^{+}	137.9 ± 3.1
Refugee's Camp	124.6 ± 9.1^{+}	122.6 ± 4.4^{+}
Triglycerides		
City	130.0 ±17.6	157.3 ± 7.8
Village	119.5 ±14.6	172.1 ± 8.8*
Refugee's Camp	110.8 ±25.6	169.4 ± 17.3

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from city values at $p<0.05$

Data presented in table 15, shows the mean levels of total cholesterol, LDL cholesterol, HDL cholesterol, and fasting triglycerides.

NIDDM population showed no significant differences in respect to triglycerides and HDL-cholesterol levels among the three categories (city, village and camp). Total and LDL-cholesterol levels were significantly lower in NIDDM patients living in the refugee camps compared to those living in either city or village.

Cholesterol and triglycerides levels where similar among non-diabetic population in all residential areas. HDL-cholesterol levels were significantly higher among non-diabetic refugee camps subjects compared to those living in either village or city. Among these categories, city inhabitance showed significantly high LDL-cholesterol levels.

3.7 Employment Status

Participants were classified to employed, unemployed, outdoors labor or housekeeper. The general characteristics and lipid profiles among NIDDM and non-diabetic populations according to employment status are shown in tables 16 and 17.

Table (16) - General characteristic of NIDDM and Non-diabetic populations according to employment status

	Non-Diabetic (49)	NIDDM (323)
BMI		
Unemployed	28.2 ± 2.5 (6)	28.7 ± 0.5 (68)
Employed	30.3 ± 1.3 (10)	28.7 ± 0.7 (21)
Outdoor labor	29.1 ± 1.6 (6)	29.0 ± 0.7 (52)
House keeper	31.9 ± 1.0 (27)	32.1 ± 0.4 (182) +
Bp – syst (mmHy)		
Unemployed	135.0 ± 9.6	140.5 ± 2.6
Employed	127.0 ± 3.9	132.0 ± 4.0
Outdoor labor	126.0 ± 8.1	136.0 ± 2.2*
House keeper	126.0 ± 2.2	137.4 ± 1.4*
Bp - Dias (mmHy)		
Unemployed	86.7 ± 3.3	85.4 ± 1.3
Employed	81.7 ± 1.9	84.0 ± 2.7
Outdoor labor	86.0 ± 4.0	82.6 ± 1.0
House keeper	83.6 ± 1.5	82.9 ± 0.7

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
+ Denotes significance from unemployed values at $p<0.05$

Housekeepers were represent by (56%) and (55%) of NIDDM and non-diabetics subjects, respectively. Among this category BMI was significantly higher compared to other employment categories of NIDDM patients. Both housekeepers and outdoor labors of NIDDM population showed a significant increase in their systolic pressure compared to the same categories of non-diabetic population.

Table (17) – Plasma lipids and lipoproteins of NIDDM and Non-diabetic populations according to employment status

	Non-diabetic(49)	NIDDM(323)
FBG		
Unemployed	79.2 ± 5.0 (6)	157.8 ± 7.5*(68)
Office employee	87.6 ± 3.2 (10)	164.4 ± 10.5*(21)
Outdoor labor	96.0 ± 13 (6)	185.0 ± 8.0*(52)
House keeper	84.8 ± 2.0 (27)	194.0± 5.2*+(182)
Cholesterol		
Unemployed	228.8 ± 21.4	218.3 ± 5.7
Office employee	193.9 ± 12.0	226.1 ± 9.5*
Outdoor labor	202.0 ± 15.2	218.5 ± 6.0
House keeper	207.0 ± 6.2	221.3 ± 3.5*
HDL-cholesterol		
Unemployed	48.3 ± 4.3	36.3 ± 1.0*
Office employee	40.0 ± 3.4	39.8 ± 1.9
Outdoor labor	36.3 ± 2.4^{+}	38.5 ± 1.2
House keeper	46.8 ± 2.0	40.4 ± 0.6*
LDL-cholesterol		
Unemployed	146.3 ± 19.5	136.5 ± 5.0
Office employee	127.7 ± 9.3	140.1 ± 7.7
Outdoor labor	133.8 ±16.0	130.3 ± 4.4
House keeper	128.9 ± 5.5	134.4 ± 2.7
Triglycerides		
Unemployed	107.2 ± 11.5	163.3 ± 13.1*
Office employee	151.8 ± 23.1	155.0 ± 14.0
Outdoor labor	178.0 ± 78.5	176.0 ± 16.4
House keeper	107.5 ± 8.9	166.0 ± 7.9*

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from Non-Diabetic values at $p<0.05$*
$^{+}$ Denotes significance from unemployed values at $p<0.05$

Among NIDDM, housekeepers showed a significant increase in their FBG compared to other employment categories. It was also found that NIDDM subjects of all categories were with slight differences in their mean levels with respect to total Cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Among non-diabetic population, the only significant difference was observed for

HDL-cholesterol among housekeepers and unemployed when compared with outdoor labor.

3.8 Family History of NIDDM

Data presented in table (18) clearly shows that a high percentage of NIDDM had family history of the disease. This is also clear irrespective of age. No gender differences were observed.

Table 18- Percent of NIDDM Participants with Diabetic Parent(s), by Age and Sex

	35 – 50 years (68)	51 – 60 years (106)	➢ 60 years (140)
Male (%)	83.8	75.0	60.3
Female (%)	80.5	71.5	61.7

3.9 Complications of NIDDM

Data presented in table 19 shows the most common complication seems to be associated with NIDDM in our study. These were represented by; 28%, 24%, 19% and 4% for nephropathy, retinopathy, IHD and neuropathy, respectively. These complications go hand to hand with duration of diabetes.

Table 19 - Duration of NIDDM and its Complications

Distribution of Complications	*Duration of NIDDM (years)*				
	0-4	*5-9*	*10-14*	*15-19*	*20-27*
NIDDM (cases)	187	98	24	8	4
Retinopathy (%)	24	30	46	13	.....
Nephropathy (%)	28	36	25	50	50
Neuropathy (%)	4	4	17	25	25
Ischemic Heart Disease (%)	19	22	8	50	50

3.10 NIDDM Therapies

Data presented in table 20 shows the therapeutic regimens as reported by NIDDM patients. Oral hypoglycemic agents, insulin, combination (insulin and oral agents) and on diet were represented by 58%, 24%, 11%, and 7%, respectively.

Table (20)- Therapies used by NIDDM population

Therapies Used	*Percentage (%)*
Use oral agents	190 (58)
Use insulin	77 (24)
Use combination	34 (11)
Follow a diabetes diet	22 (7)

Data presented in table 21 clearly shows that BMI significantly increased among those who were on either combined therapy or oral agent when compared with those on insulin alone.

Table (21)- Characteristics of NIDDM population according to therapies used

	Oral agents (190)	Insulin (77)	Combination (34)	Diet (22)
Age	58.6 ± 0.7	60.9 ± 1.0	59.3 ± 1.3	58.8 ± 2.8
Bp Dias(mmHg)	83.8 ± 0.7	82.8 ± 1.0	81.2 ± 1.6	84.4 ± 1.7
Bp Syst(mmHg)	138.5 ± 1.4	136.5 ± 2.0	136.3 ± 3.5	136.1± 3.4
BMI (Kg/m^2)	31.2 ± 0.4 *	28.8± 0.5	31.8 ± 0.9 *	30.6 ±0.3

Data are means ± SE for the number of cases appears in parenthesis.
** Denotes significance from values of insulin use at $p<0.05$*

Data presented in Table 22 shows that combined treatment was associated with a significant increase in FBG when compared with diet or oral agent regimes.

Table (22)- Blood lipids and lipoproteins profile in NIDDM population according to therapies used

	Oral agents (190)	Insulin (77)	Combination (34)	Diet (22)
FBG	176.9 ± 4.4*	191.5 ± 7.9	207.3 ± 14.5*	170.6 ± 14.9*
Cholesterol	217.5 ± 3.2	225.8 ± 6.0	223.7 ± 8.0	222.6 ± 9.0
LDL–Cholesterol	131.4 ± 2.6	136.2 ± 4.7	136.9 ± 6.1	142.0 ± 10.0
HDL–Cholesterol	40.3 ± 0.9	39.9 ± 2.0	38.2 ± 1.5	39.1 ± 2.2
Triglycerides	164.4 ± 7.3	162.9 ± 11.8	182.9 ± 25.3	175.4 ± 18.4

Data are means ± SE for the number of cases appears in parenthesis.
** denotes significance from values of oral agents and diet*

Chapter IV

DISCUSSION

Since we are dealing with NIDDM patients one should expect that the majority of the participants were of the elderly group. In our study, the subjects aged between 35 to 73 with a mean age of 56.5±o.5 and over 75% were over 50 years old. Out of 323 NIDDM studied subjects, females were represented by 59%. Percentage differences between affected males and females could be partly due to the fact females are over represented in our community, specially at 50 years and over (59). Another possible explanation is BMI, which is considered as one of the major risk factors (33, 42, 77, 80) for the development of NIDDM (28.5 for males and 32.1 for females) as shown, in table 8. It is worth noting, that the role-played by men in our community completely differs from that for women and that may also explain such findings and this can be deduced from the observations on housekeepers general characteristics (see table 16).

Strong epidemiological links exists between NIDDM and obesity (16, 17). Westernized lifestyle including sedentary lifestyle, physical activities and diet were accused in developing NIDDM (12,14,23). In such countries, diets are usually low in their fiber content, carbohydrate and high fat content than traditional diets (13, 14, 15,). Unfortunately, data regarding diets in our community are

lacking and that was one of the main obstacles that faces is in our study and we were unable to relate this to any of our findings in this respect.

In our study, overweight with BMI >27 and obese with BMI >30 among NIDDM patients were represented by 74% and 53%, respectively. This finding is in support of previous published data concerning NIDDM risk factors (16, 17). Increased BMI is known to reflect diabetes severity as indicated by blood parameters (table 5). Similar findings on blood parameters were reported in a study conducted in neighboring Jordan (77). The findings in table 5 regarding the various blood parameters are in agreement with previous reports, with triglycerides and HDL being the most affected parameters (25, 27, 28, 29, 31, 32, 33). This is also in agreement with data presented in table 7, which showed a summary of all changes regarding the behavior of the various parameters among NIDDM patients.

The mechanism of hypertension in diabetic patients is poorly understood and may involve a complex interaction between inherited factors that predispose the development of high blood pressure and the metabolic abnormalities (36, 37, 38). Several mechanisms have been reported, of which insulin resistance and hyperinsulinemia seems to contribute to hypertension through its

effect on sodium retention and activation of sympathetic nervous system and many other pathways (36, 37, 38). Our findings regarding hypertension status indicates a positive correlation between hypertension and diabetes as 51% of NIDDM patients showed increased blood pressure, thus, our findings are in agreement with previous reports in this regard (36, 37).

Diabetes mellitus is associated with a considerable increase risk of premature arteriosclerosis, particularly coronary artery disease and peripheral arterial disease. The risk of atherosclerosis within the diabetic population is not directly linked to blood glucose however, a much stronger association is linked with serum lipid levels, both in serum cholesterol and in particular triglycerides. The risk of IHD is greater at any given level of serum cholesterol in diabetes as opposed to the non-diabetic population (25, 28, 29, 31). This is probably related to the abnormal lipoprotein metabolism in NIDDM (30, 34). Our data is consistent with the above-mentioned behavior of lipid profiles, especially that of triglycerides and both total and HDL- cholesterol when compared with non-diabetic group as shown in table 6. Based on international criteria one cannot rely on triglycerides and both total and HDL- cholesterol to predict the role and association of such compounds and the risk of IHD, however, they can be considered as indicators for IHD.

Our data shows that NIDDM women have higher HDL-cholesterol level compared to that for men (see table 9). On the other hand cholesterol, triglycerides and LDL-cholesterol were similar. Such finding is consistent with several reports (25, 33, 42, 75).

The observed increased levels of both systolic and diastolic pressure in our results is consistence with other previous reports. Both parameters in addition to hypertension prevalence seem to increase with age (32, 36, 37).

A positive association was observed between BMI and age (80), but was negatively associated with the duration of diabetes (75). Al-sha'ar *et al.*, showed that BMI was slightly decreased with increasing age in diabetic patients with a long duration of diabetes in Nablus district (59). In our study a positive correlation between BMI and age was observed up to age of 60, however, negative association observed thereafter. This could be a consequence of aging or prolonged disease duration.

Low levels of total and LDL-cholesterol among NIDDM patients inhabiting refugee camps compared to those living in either city or village is most likely reflecting differences in lifestyle.

Parental history of diabetes is well-documented (81,82). Family history of diabetes is reported much more frequently in

subjects with a medical history of NIDDM (82). The National Health and Nutrition Examination Survey (NHANES) showed that 46.6% of those with a medical history of diabetes at age 20-54 years have a parent with diabetes (82). The observed high percentage of NIDDM subjects with diabetic parent emphasizes the role of genetic factors and requires further investigation.

Recommendations and Suggestions for Further Study

1. Careful monitoring of NIDDM patients on routinely basis.
2. Specially designed programs at the national level seems to be essential, such program should be targeted towards risk factors and preventive measures.
3. Studies on diets, BMI, environmental and lifestyle, being recognized as major risk factors, are necessary and should include all NIDDM as well as high risk groups.
4. Case control study should provide a better understanding of the underlying factors associated with the disease and its complications.

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ملخـــص

لقد تمت دراسة العوامل المحيطة بمرض السكري من النوع الثـاني (NIDDM) في محافظة نابلس – فلسطين . حيث تم اختيار عينة عشوائية منتظمة تتكون مـــن 323 مريض من ثلاث عيادات سكري تابعة لوزارة الصحة الفلسطينية ووكالة الغوث الدوليـة (UNRWA) ، ومع أن الدراسة ضمت 49 شخص طبيعي (non- NIDDM) إلا أنـــها لا تعتبر دراسة مقارنة .

أظهرت الدراسة بأن كلتا العينتين (NIDDM و non-NIDDM) تتميز بالســـمنة حيث أن مؤشر السمنة (BMI) كان أكثر من 30 Kg/m^2 لكل منهما .

وكما هو متوقع فان الدراسة أظهرت ارتفاعا في كل من دهنيـــات الكلســترول الكلـي (Cholesterol) والدهنيات الثلاثية (Triglycerides) لمرضى السكري وانخفاضا ممـــيزا في (HDL - C) عن المعدل الطبيعي له .

كذلك أظهرت الدراسة أن الإناث تميزت بارتفاع أل (BMI و HDL- C) مقارنـة بالذكور . لوحظ أيضا وجود علاقة طردية بيـــن ارتفـاع ضغـط الـدم الانقبـاضي (Systolic Blood Pressure) مع ازدياد العمر .

لقد أظهرت الدراسة ارتفاعا في مؤشر السمنة (BMI) وضغط الـدم الانقبـاض (Systolic Blood Pressure) وانخفاضا في تركيز الكلســترول الكلـي و LDL – C للمرضى القاطنين في المخيمات مقارنة بالقاطنين في المدينة أو القرية .

أظهرت الدراسة أيضا ارتفاعا في تركيز HDL – C وانخفاضا فـــي LDL – C للعينة غير المريضة (non- NIDDM) والقاطنة في المخيمات مقارنة بالمدينة .

لقد بينت الدراسة أن 81% من مرضى السكري عندهم تاريخ عائلي بـــالمرض وهذه النسبة تتناقص مع ازدياد العمر لتبلغ 62% لمن هم بعمر 60 سنة فما فوق .