T.C
YEDITEPE UNIVERSITY
GRADUATE INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PHARMACOECONOMY AND PHARMACOEPIDEMIOLGY

A STUDY INVESTIGATING USAGE OF VITAMIN B SUPPLEMENTATION AND CURRENT SERUM VITAMIN B LEVELS OF ELDERLY PATIENTS WITH CHRONIC DIABETES MELLITUS RESIDED IN ALMSHOUSE

MASTER THESIS

PHARMACIST
TUĞÇE ALTIOK RUSSO

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Prof. Dr. Bayram YILMAZ
Director of Institute of Health Sciences

DEDICATION

to my family and Roberto …

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LIST OF ABBREVIATONS

AGEs: *Advanced Glycosylated End Products*

CBL: *Cobalamin*

CVD: *Cardiovascular Disease*

DM: *Diabetes Mellitus*

DN: *Diabetic Nephropathy*

ESRD: *End-Stage Renal Disease*

HbA1c: *Hemoglobin A1c*

MI: *Myocardial Infarction*

MNT: *Medical Nutritional Theraphy*

ROS: *Reactive Oxygen Species*

SPSS: *Statistical Package for Social Sciences*

T2DM: *Type 2 Diabetes Mellitus*

TURDEP: *The Turkish Diabetes Epidemiology Study*

UACR: *Urine Albumin-to-Creatinine Ratio*

ABSTRACT (ENGLISH)

Russo T.A. (2015). A Study Investigating Usage Of Vitamin B Supplementation And Current Serum Vitamin B Levels Of Elderly Patients With Chronic Diabetes Mellitus Resided In Almshouse. Yeditepe University, Institute of Health Sciences, Department of Pharmacoeconomy and Pharmacoepidemiology, MSc Thesis, Istanbul.

Diabetes Mellitus (DM) is one of the most common chronic diseases worldwide. It is assumed that diabetic complications can occur as a result of vitamin B deficiency and B vitamins can alleviate some symptoms of diabetic neuropathy. The main aim of this study is to investigate the relationship between vitamin B supplementation and the current serum vitamin B levels in elderly. The study was conducted in Darülaceze Almshouse Kayışdağı Campus and was continued from May 2012 to September 2012. Within the scope of mixed method, data filtering technique and Neuropathic Symptoms & General Satisfaction of Patients Assesment Form were applied to 110 elderly with diabetes. By using data filtering technique from the automation system, demographic characteristics and changes in the serum vitamin B12, folate and plasma HbA1c levels of 110 elderly with diabetes were investigated. A majority of the population (2/3) were males in an elderly population with mean 69 years of age. There is no significant difference in HbA1C levels in patients the ones using and not using vitamins ($p>0.05$). However, significance exists in terms of B12 and folic acid designated by Mann Whitney U test. Also, Wilcoxon Test had been used to explore the statistical differences between the evaluations before and after treatment. No significant difference has been found for HbA1c and Folic acid values ($p>0.05$). However, there was a significant increase in B12 ($p<0.05$) concentration after treatment indicating a positive streamline for the individuals. 64.5 % of the participants (n=71) responded their patient satisfaction as good, 28.2 % (n=31) admitted as moderate. This investigation reveals current evidence is not strong enough for supplementation with vitamins to be recommended for DM management. Double-blind and randomized controlled trials are needed to confirm the clinical effectiveness of vitamin B usage on diabetes.

Key Words: *Elderly, Vitamin B Deficiency, Neuropathy, Diabetes Mellitus*

ABSTRACT (TURKISH)

Russo T.A. (2015). Yaşlı Bakım Evinde İkamet Eden Kronik Diyabet Hastalarının B Vitamini Kullanımı ve Serum B Vitamini Düzeyleri Arasındaki İlişkinin İncelendiği Bir Araştırma. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Farmakoekonomi ve Farmakoepidemiyoloji BD., Master Tezi, İstanbul.

Diabetes Mellitus (DM) dünya genelinde en çok gözlenen kronik hastalıktır. Diyabete bağlı komplikasyonların B vitamini eksikliği sonucunda ortaya çıkabileceği ve B vitamini kullanımının diyabetik nöropati semptomlarını azalttığını gösteren çalışmaların olduğu bilinmektedir. Bu çalışmada yaşlı bakım evinde ikamet eden kronik diyabet hastalarının B vitamini kullanımı ve B vitamini düzeyleri arasındaki ilişki incelenmiştir. Darülaceze Kayışdağı Kampüsü'nde Mayıs – Eylül 2012 döneminde gerçekleştirilen çalışmanın verileri karışık metot yöntemi ile elde edildi. Veri filtreleme tekniği ve hasta memnuniyetinin ölçümlendiği nöropati semptomu değerlendirme form uygulaması diyabetli 110 yaşlı sakin için uygulandı. Otomasyon sisteminden, veriler çekilerek demografik özellikler ve serum vitamin B12, folik asit ve HbA1C düzeylerindeki değişiklikler incelendi. Araştırmaya katılanların üçte ikisi erkek, ortalama yaşları ise 69'dur. Mann WhitneyU testi ile vitamin kullanan ve kullanmayan hastaların HbA1c düzeyleri arasında anlamlı bir fark bulunmazken ($p>0,05$); B12 vitamini ve folik asit yeni düzeyleri arasında anlamlı bir fark bulunmuştur ($p<0,05$). Wilcoxon testi ile vitamin kullanan kişilerin hem HbA1c eski ile HbA1c yeni ölçümlerinde hem de folik asit eski ve folik asit yeni ölçümleri arasında istatistiksel olarak anlamlı fark bulunmazken ($p>0,05$); B12 vitamini eski ile B12 vitamini yeni ölçümleri arasında anlamlı yükseliş gözlenmiştir ($p<0,05$). Hastaların % 64,5'inin hasta memnuniyet düzeyleri iyi, %28,2'sinin ise orta düzeydedir. Bu çalışma diyabet yönetimi için B vitamini takviyesinin kullanımının önerilmesi için mevcut kanıtların yeterli olmadığını göstermektedir. B vitamini destek tedavisinin diyabetteki rolünün ortaya konulabilmesi için çift-kör, randomize ve kontrollü klinik çalışmaların yapılmasına ihtiyaç duyulmaktadır.

Anahtar Kelimeler: *Yaşlı, Vitamin B eksikliği, Nöropati, Diyabet*

1. INTRODUCTION

The term diabetes mellitus (DM) describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both(1). As mentioned below, DM is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar (2). Insulin allows cells and tissues of the body to take up glucose and use it or store it, thus reducing the levels of glucose in the bloodstream after a meal. A lack of insulin causes glucose in the blood to remain high and these high blood glucose levels are responsible for the damaging complications of diabetes. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

The classification of diabetes includes four clinical classes (3):

● Type 1 diabetes (results from -cell destruction, usually leading to absolute insulin deficiency): It is an autoimmune disease. Due to loss of self-tolerance, the immune system destroys the insulin-producing cells of the pancreas and accounts for 3–5% of all diabetes cases globally. It commonly develops in children and the young, although it is possible to develop type 1 diabetes in adulthood.

● Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance): It is due to a combination of insulin secretory defects and resistance to the actions of insulin at the tissue levels of different organs. It is the most common type of diabetes, accounting for 95% or more of all diabetes cases globally. It most commonly occurs in middle-aged and older people but is increasingly affecting overweight children,

adolescents and young adults.

● Other specific types of diabetes due to other causes, e.g., genetic defects in-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)

● Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes): It is glucose intolerance with onset or first detection during pregnancy and affects at least one in 25 pregnancies globally. Women with gestational diabetes and the offspring of these pregnancies are also at increased risk of developing type 2 diabetes later in life.

Diabetes mellitus may present with characteristic symptoms such as:

- ✓ thirst,
- ✓ polyuria,
- ✓ blurring of vision, and
- ✓ weight loss.

In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Often symptoms are not severe , or may be absent, and consequently hyperglycemia of sufficient degree to cause pathological and functional changes may be present for a long time before the diagnosis is made. The long-term effects of diabetes mellitus include:

- ✓ progressive development of the specific complications of retinopathy with potential blindness,
- ✓ nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation,
- ✓ charcot joints, and features of autonomic dysfunction, including sexual dysfunction.

- ✓ People with diabetes are at increased risk of cardiovascular, peripheral vascular, and cerebrovascular disease (1).

In the near future, the majority of patients with diabetes will be adults aged 65 or older. Elderly diabetic people may be affected by a variety of comorbid conditions such as depression, urinary incontinence, cognitive impairment, muscle weakness (sarcopenia), injurious falls, and physical frailty than other older persons (4). In addition to these conditions, premature death, functional disability, and concurrent illnesses such as hypertension and coronary heart disease should take into consideration for elderly with DM. Primary care givers should be aware of these functional problems in this specific population. This awareness is crucial because, the identification and management of these syndromes may ameliorate the effectiveness of DM management.

Aims of DM care in elderly should be set according to the motivation, combined diseases, presence of complications, resources, support system, and life expectancy of each individual patient. It is well established that the risk of microvascular and macrovascular complications is related to glycemia, as measured by HbA1c; this remains a major focus of therapy (5). The California Healthcare Foundation/ American Geriatric Society Panel on Improving Care for Elders with Diabetes suggested that a reasonable goal for hemoglobin A1c (HbA1c) in relatively healthy elderly with good functional status should be 7% or lower. For frail adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefits, a less stringent target of 8% was recommended (4). As is the case with younger people, the targets of DM management in elder adults should cover control of hyperglycemia and its symptoms; prevention, assessment, and therapy of macrovascular and microvascular complications of DM; DM self-management through education; and maintenance or enhancement of overall well-being. Although these goals are identical in older and younger persons, elderly care is complicated by their clinical and functional heterogeneity.

On the other hand, quality of life is another crucial consideration in maintenance of elderly with DM. Although several interventions have been found to significantly reduce morbidity and mortality, it is clear that the potential benefits may be associated with reduced quality of life in older adults, particularly for those with chronic conditions (6). Clearly, complicated, pricey, or distressing treatment procedures may result in destructive adverse effects, reduction in compliance to suggested therapies, and a decline in overall well-being. The achievable effects on quality of life should be taken into account in any treatment strategy.

1.1. Epidemiologic Data

Diabetes Mellitus is one of the most common chronic disease and its complications remain major causes of morbidity and mortality worldwide. It is increasingly impacting individuals, families and society as the disease affects more and more people. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8 % in 2000 and 4.4 % in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (7). World Health Organization (WHO) projects that diabetes will be the 7th leading cause of death in 2030. The 15 leading causes of death is listed according to the baseline scenario for males, females, and both sexes combined as projected for 2030 globally (Table 1) (8).

The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age (7). In the population over 65 years of age, the estimate is even more alarming: 10.9 million people or 26.9% of all people in this age group suffered from diabetes in 2010 (9). As is known, increasing age is a risk factor for the development of DM and for the development and progression of the complications of DM.

The increasing prevalence of diabetes goes hand in hand with an ageing population and changing lifestyles. As the population of Turkey gets older and life expectancy increases, even more people will be affected by type 2 diabetes and other chronic diseases. Over the past decade and a half in Turkey, two national surveys have been done to establish how many people are living with diabetes or are at risk of developing the condition. The first survey, The Turkish Diabetes Epidemiology Study-I (TURDEP-I), took place in 1997 and 1998 and was followed up by TURDEP-II in 2010. According to the two population-based diabetes surveys in Turkey performed in 1998 and 2010, the prevalence of diabetes increased by almost 90% among adults and continues to rise. Both surveys collected data from the same 540 centres using the same methodology to allow for comparison of results (10, 11).

The TURDEP-I is an important source of data from on diabetes and risk factors which shows that crude prevalence of diabetes was 7.2% (previously undiagnosed, 2.3 %) and of impaired glucose tolerance (IGT), 6.7% (age-standardized to world and European populations, 7.9 and 7.0 %) in 1998 for Turkey (10). The TURDEP-II survey is one of the largest nationally representative diabetes surveys carried out in Turkey. The survey shows that diabetes is rapidly becoming a major public health challenge for the country. The study aimed to determine the prevalence of diagnosed and undiagnosed diabetes, prediabetes and their 12-year trends, and to identify risk factors for diabetes in the adult Turkish population. The study invited 26.499 people from these centres to take part, of which 87% agreed to participate in the research (11). As a conclusion, between the 12 years period of these two largest epidemiologic data, frequency of diabetes increased 90% and of obesity 44%. DM seems to start 5 years earlier comparing with the previous estimation (10, 11).

Table 1. Changes in Rankings for 15 Leading Causes of Death, 2002 and 2030 (Baseline Scenario) (8)

Income Group	Rank	Disease or Injury	Percent of Total Deaths
World	1	Ischaemic heart disease	13.4
	2	Cerebrovascular disease	10.6
	3	HIV/AIDS	8.9
	4	COPD	7.8
	5	Lower respiratory infections	3.5
	6	Trachea, bronchus, lung cancers	3.1
	7	Diabetes mellitus	3.0
	8	Road traffic accidents	2.9
	9	Perinatal conditions	2.2
	10	Stomach cancer	1.9
High-income countries	1	Ischaemic heart disease	15.8
	2	Cerebrovascular disease	9.0
	3	Trachea, bronchus, lung cancers	5.1
	4	Diabetes mellitus	4.8
	5	COPD	4.1
	6	Lower respiratory infections	3.6
	7	Alzheimer and other dementias	3.6
	8	Colon and rectum cancers	3.3
	9	Stomach cancer	1.9
	10	Prostate cancer	1.8
Middle-income countries	1	Cerebrovascular disease	14.4
	2	Ischaemic heart disease	12.7
	3	COPD	12.0
	4	HIV/AIDS	6.2
	5	Trachea, bronchus, lung cancers	4.3
	6	Diabetes mellitus	3.7
	7	Stomach cancer	3.4
	8	Hypertensive heart disease	2.7
	9	Road traffic accidents	2.5
	10	Liver cancer	2.2
Low-income countries	1	Ischaemic heart disease	13.4
	2	HIV/AIDS	13.2
	3	Cerebrovascular disease	8.2
	4	COPD	5.5
	5	Lower respiratory infections	5.1
	6	Perinatal conditions	3.9
	7	Road traffic accidents	3.7
	8	Diarrhoeal diseases	2.3
	9	Diabetes mellitus	2.1
	10	Malaria	1.8

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Both the prevalence and incidence of type 2 diabetes are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernization of lifestyle. The attendant economic burden for health care systems is skyrocketing, owing to the costs associated with treatment and diabetes complications (12). Diabetes is estimated to have cost USD 548 billion in health spending in 2013, 11% of the total spent on health world wide. By 2035, this number is projected to exceed USD 627 billion (13).

1.2. Long-term complications of Diabetes Mellitus (DM)

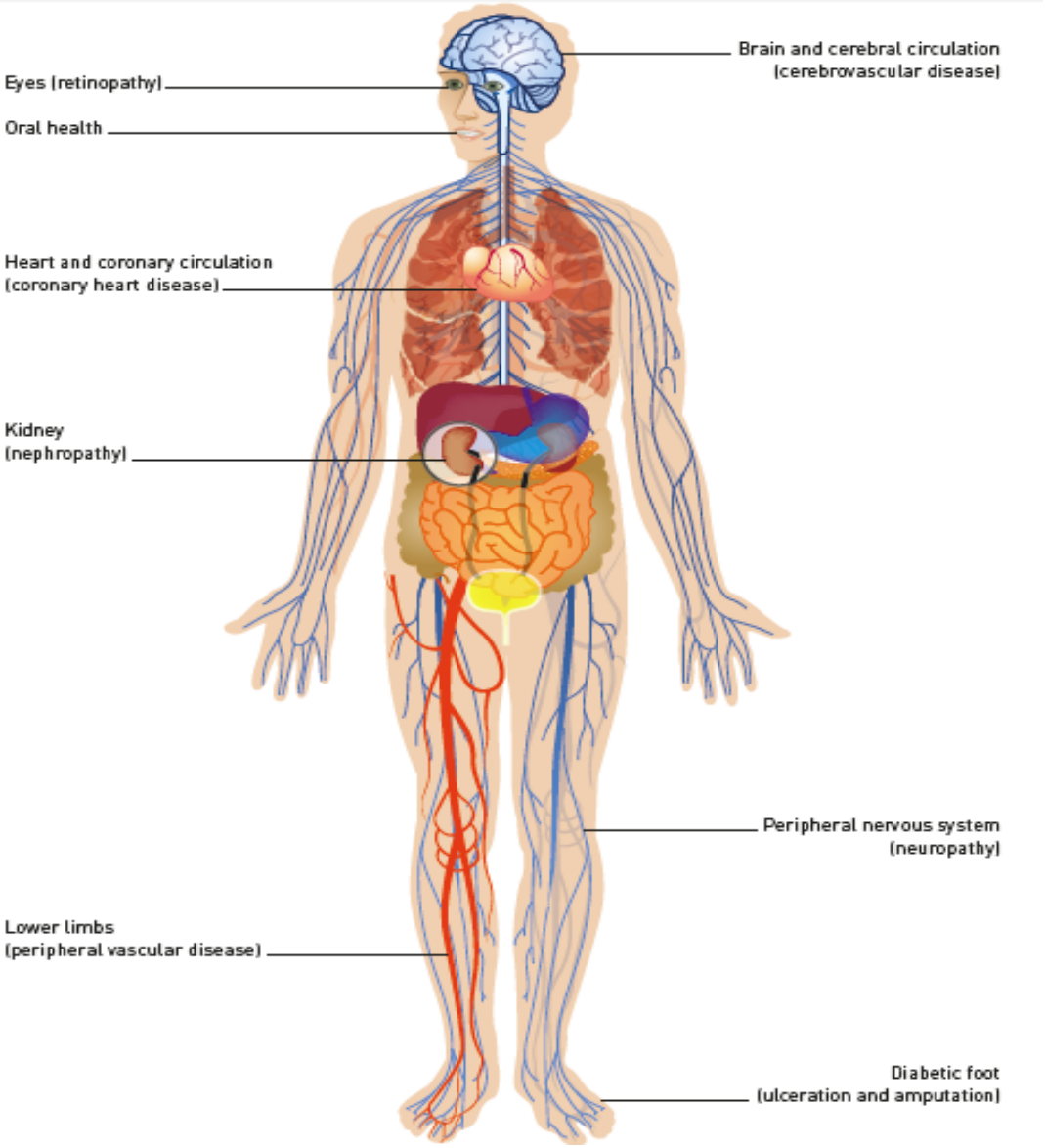
Diabetic patients are at risk of establishing a certain number of damaging and life-threatening health issues. Persistently high blood glucose levels may cause serious illnesses affecting the heart and blood vessels, eyes, kidneys, and nerves. In addition, these patients are at expanded risk of emerging infections. Nearly in all high-income countries, DM is an outstanding origin of cardiovascular illness, blindness, kidney failure, and lower-limb amputation. Untreated or poorly treated diabetic patients may have the possibility of these serious complications (14).

Chronic hyperglycemia is the considerable initiator of vascular complications of DM. The influence of defending the body from hyperglycemia cannot be extenuated; the direct and indirect consequences on the human vascular tree are the major origin of morbidity and mortality in both type 1 and type 2 diabetes mellitus. Ordinarily, the destructive effects of hyperglycemia are divided into macrovascular complications (cardiovascular diseases; etc. coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic neuropathy, nephropathy and retinopathy) (13) (Figure 1).

- **Cardiovascular disease (CVD):** CVD is the major cause of death and disability among diabetic patients. This kind of disease that leads diabetes cover angina, myocardial infarction (MI), peripheral artery disease, and congestive heart failure. In diabetic patients; augmentation of blood pressure, cholesterol, blood glucose and other risk factors may promote the expanded risk of cardiovascular complications. A number of clinical researches have demonstrated the efficacy of controlling personal cardiovascular risk factors in preventing or getting slower CVD in diabetic patients. Broad advantages are identified when various risk factors are oriented globally (15, 16). In addition, hypertension is also a familiar diabetes comorbidity that influences the generality of patients, with the prevalence based on form of diabetes, age, obesity, and ethnicity. Hypertension is a leading risk aspect

for both CVD and microvascular complications. It is generally the consequence of underlying nephropathy in type 1 diabetes, while in type 2 diabetes it often coexists with other cardiometabolic risk aspects. Moreover, dyslipidaemia may be associated with the occurrence microvascular complications (13).

Figure 1. The major diabetes mellitus complications (13)



Diabetic vascular complication is a leading origin of end stage renal failure, acquired blindness, a number of neuropathies and speeded atherosclerosis, that may clarify defects and high death rates in people with diabetes (17). Microvascular illness related with diabetes in the retina, glomerulus and vasa nervorum may have common pathophysiological properties. Early in the course of diabetes, intracellular hyperglycaemia causes abnormalities in blood flow and increased vascular permeability (18). Duration and magnitude of hyperglycemia are both strongly correlated with the extent and rate of progression of diabetic microvascular disease.

The pathogenesis of vascular complications in diabetes is a disputed topic and despite a comprehensive study no integrative mechanism has been determined.

Several hypotheses states that:

- ✓ capillary hypertension,
- ✓ insulin resistance syndrome,
- ✓ endothelial dysfunction,
- ✓ augmented vascular inflammation ,
- ✓ oxidative stress with enhanced glycation end product (AGE) formation (18).

- **Diabetic neuropathy:** It is the most common of the microvascular complications related with DM and a few type of nerve disorder (etc. the decelerating of conduction speed, pain, sensory loss and fiber degeneration) is supposed to emerge in approximately half of the people with diabetes. Loss of sensation in the extremities to pain and other improper sensations are generally the primary manifestations of diabetic neuropathy and neuropathic pain is expected to develop in 5–15% of people with diabetes (19). Painful neuropathy is a familiar and disabusing issue in long-lasting diabetic patients. Other vascular complications such as low metabolic control, dyslipidemia, hypertension, body mass index (BMI), smoking, microalbuminuria and retinopathy are also related with diabetic neuropathy as risk factors (17). Especially neuropathic pain, which is one of the

common symptoms of diabetic peripheral neuropathy, may be severe, have quick onset of action, and leads a decrease in quality of life, limitation of mobility, depression, and social dysfunction (14). This complication can give rise to problems with digestion and urination, erectile dysfunction and various of other functions. The extremities, particularly the feet may be affected normally. Nerve deterioration in these parts of the body is termed peripheral neuropathy, and can result with pain, tingling, and loss of feeling. Loss of feeling may be especially critical because it may permit degenerations to go overlooked, leading to severe infections and ulceration, diabetic foot illness, and major amputations. Rigid glycemic control is the only policy definitely shown to prevent or postpone the the progress of diabetic neuropathy.

- **Diabetic nephropathy:** It is the leading origin of end-stage renal disease (ESRD) and accounts for disabilities and the high mortality rate in patients with diabetes. Hyperglycemia, augmented blood pressure levels, and genetic predisposition are the essential risk aspects for the occurrence of diabetic nephropathy. This complication is caused by damage to small blood vessels, which can result the kidneys to be less efficient, or to fail together. It has been termed as augmented protein excretion in urine. Constant increased albuminuria level in the scope of urine albumin-to-creatinine ratio (UACR) 30–299 mg/g is an early indicator of diabetic kidney disease in type 1 diabetes and a marker for development of diabetic kidney disease in type 2 diabetes. It develops in 20–40 % of diabetic patients (14). Diabetic nephropathy in people with type 1 DM, is originally described by a clotting of the glomerular and tubular basal membrane, with continuous mesangial development leading to the progressive declining of the glomerular filtration surface. It is indicated by glomerular hyperfiltration in the struggle of the afferent and efferent glomerular arterioles, and consequent augmented renal perfusion (20). It can be crucial to determine the stage of diabetic nephropathy (microalbuminuria, proteinuria or GFR) for and the result of interest for treatment strategy. Keeping blood glucose and blood pressure levels close to normal can greatly decrease the

risk of nephropathy.

- **Diabetic retinopathy:** It can impair vision or aggravate blindness and it is one of the most familiar microvascular complications of DM and graded as a typical cause of blindness worldwide (21). Diabetic retinopathy could develop a risk aspect for individuals due to the global prevalence of DM, that is predicted to influence 438 million people by 2030 (13). Both the duration of diabetes and its metabolic control have been identified as the risk factors most strongly associated with the occurrence of retinopathy. It emerges in 70% of all diabetic patients for more than 15 years. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in diabetic patients. Increase in blood glucose, blood pressure and cholesterol levels are the fundamental causes of diabetic retinopathy. It is identified by the occurrence of vascular lesions of increasing severity, concluding in the improvement of different vessels (21). The network of blood vessels that supply the retina can become blocked and damaged in retinopathy, leading to permanent loss of vision. It can be maintained through regular eye examinations and by sustaining blood glucose levels close to normal.

Sustaining blood glucose levels as near to the non-diabetic scope as achievable has been showed to have a impressive valuable impact on diabetes-specific complications, including retinopathy, nephropathy and neuropathy in the context of type 1 diabetes; in type 2 diabetes, more comprehensive treatment regimens have similarly been showed to diminish complications.

1.3. Effects of Diabetes Mellitus (DM) in elderly people

Diabetes Mellitus (DM) may develop in everyone. Nonetheless, individuals who have close relatives with DM are more similarly to occur it. Other risk factors include obesity,

high cholesterol, high blood pressure, and physical inactivity. The risk of emerging DM also rises in in people who are over 40 years old (13, 22).

Diabetic elderly patients are at augmented risk of some type of functional degeneration concluding from diabetes complications. When natural aging process and other age-related conditions takes into account, DM makes a contribution to impoverished results in elderly people compared to those without diabetes.

Elderly patients are at a higher risk of hypoglycemia for many reasons, including insulin deficiency and continuous renal insufficiency. These people are also at a greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, and persistent pain. Peripheral neuropathy is seen in up to 70% of diabetic elderly patients (13, 22), development of the risk of falls and fractures (23) and alteration in glycemic cases. Diabetic patients are 1.5 times more likely to occur dementia than those without diabetes (24). Moreover, a few studies demonstrates a stable relation between diabetes and depression, that may also influence the self-care potentials of each individual (25). These elderly people are at elevated risk of inadequate nutrition and loss of skeletal mass: they have minor energy requirements and usually decreased appetite and reduced sense of thirst.

In consequences of these problems, a custom-made treatment attitude to care elderly diabetic patients is obligatory to decrease possibly severe adverse events. Comorbidities and complications need to be actively identified. Doctors should build, in collaboration with patients, special aims of care or target outcomes for people with DM. Such objectives should be described and authenticated for all conditions of management, such as administration of hypertension, hyperlipidemia, hyperglycemia, mood confusion, if exist and also monitoring and treatment of old-age related risks if present. In case of these objectives of DM management are not received, then the patient should be assessed for arising sources.

Obstacles with compliance to medications or to lifestyle adjustment may be a cause that objected results are not accomplished. Doctors should reconsider the usefulness of medication dosing and payments. Epidemiological proof demonstrates that medications may promote or aggravate geriatric problems, alone or through drug-drug and/or drug-illness interactions. Plenty of medications (particularly those with sedating effects) have been related with cognitive damage (delirium or dementia) in elderly patients (6). Definitely, adverse drug reactions have been affected in failure to thrive in elderly patients, developing in functional deterioration, deppresion, and malnutrition (26).

In addition, quality of life is the other crucial issue in management of elderly diabetic patients. Even though, various interferences have been discovered to extremely diminish morbidity and mortality, it is fair that the possible advantages may be related with decreased quality of life in elderly patients, especially for those with chronic situations. The potential benefits on quality of life should be considered in every treatment regimen.

Although it is similarly that certain guidelines may be concluded to many elderly DM patients, intensive management of all these situations concurrently may not be achievable for a ratio of elderly DM patients, and doctors may need to give priority decrease of possible risks over others.

1.4. Role of Vitamins in Diabetes Mellitus (DM) Management

Vitamins and minerals have a crucial act in glucose metabolism, comprehending the effect of vitamin and mineral insufficiencies and the achievable effectiveness of supplementation is applicable for the prevention and/or management of diabetes mellitus (DM). Vitamin supplementation shows a critical role even though it is usually disregarded throughout the DM treatment. Lifelong screening of blood glucose level, healthy nutrition, keeping in training regularly, and potentially DM medication are needed for treatment of DM.

Multi-vitamin intake may relieve a serial of diabetic symptoms such as exaggerated

tiredness, thamuria (frequent urination), and thirst. Earlier study has demonstrated that multi-vitamins support to enhance insulin action, responsiveness to stimuli; decrease insulin resistance and lower fasting blood sugar levels; relieve the acts of injurious free radicals; and improve the efficiency of glucose burning. Moreover, a few studies clarify enhancement of vision from the deleterious consequences of diabetes-related macular degeneration. For many people, multi-vitamins are an integral part of a daily routine, one of the mainstays of a regimen to foster the overall health and wellness. But for people at risk of developing diabetes, as well as for those with pre-diabetes or diabetes, taking a multi-vitamin may completely alter the rest of their life and their quality of life (27).

Especially, vitamin B takes an active role in energy metabolism. Nerve tissue may be influenced in sufficiency circumstances by reason of its “high-energy requirement or specific actions of the vitamin”. Vitamin B deficiencies are notorious for their influence on energy levels in the body. That’s because many vitamin B are cofactors required for the proper breakdown of food into energy. Cobalamin (vitamin B12), folic acid (vitamin B9), biotin (vitamin B7), pyridoxine (vitamin B6), pantothenic acid (vitamin B5), nicotinamide (vitamin B3), riboflavin (vitamin B2), and thiamin (vitamin B1) are vital B vitamins that work as coenzymes get involved in energy generating and other metabolic mechanism (28).

1.4.1. Relationship Between Vitamin B Deficiencies and Diabetic Complications

Nutritional deficiency is thought to be a considerable health concern influencing the ordinary way of life of each individual in emerging countries. Elderly diabetic patients are at specific risk for deficiencies of related nutrients. Unregulated incrementation of blood glucose level chronically may result in significant changes in the rank of the nutrients, especially those that have been identified as micronutrients, may precisely regulate glucose homeostasis. The recognition of DM at the early stage before chronic complications may enhance the quality of life and nutritional status and, diminishes the mortality. Aged-

related alterations must be considered to present the medical nutritional therapy (MNT) for diabetic patients. MNT is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of improvement of diabetes complications (29).

Familiar deficiency properties of Vitamin B consist of peripheral neuropathy, depression, mental disorientation, shortage of motor coordination, and asthenia. Beriberi (thiamine), pellagra (nicotinamide), megaloblastic anaemia (folic acid), and pernicious anaemia (cobalamin) are considered to be particular vitamin B deficiency diseases in people. The recommended daily allowances of B vitamins for a normal adult are as follows: thiamine 1.0 to 1.5 mg, riboflavin 1.2 to 1.7 mg, pyridoxine 1.4 to 2.0 mg, niacin 13 to 19 niacin equivalents; cobalamin 3 to 5 mg and folic acid 50 mg (28).

The microvascular complications of DM, concluded with a destruction of the microvasculature of the kidney, retina and neurons, include diabetic retinopathy (DR), diabetic nephropathy (DN), and neuropathy. As a result of microvascular pathology, diabetes mellitus is a crucial origin of blindness, end-stage renal syndrome and an assortment of attenuating neuropathic symptoms (13, 18).

The pathogenesis of vascular diabetic complications is a much discussed issue and regardless of considerable study no integrative mechanism has been identified. Several hypotheses are thought: capillary hypertension, insulin resistance disorder, endothelial dysfunction, development of vascular inflammation and oxidative stress with advanced glycation end product (AGE) formation. As long as, these are all essential processes it would come out that one is not privileged than the other and it is more similarly that all the above mechanisms are integrally associated (18, 29). Vitamins play as not only nutritional supplements for deficiency, but pharmacological agents for treatment. Application of vitamins to diabetic patients diminish insulin needs and attracts much attention for improvement of vascular complications (31).

Dysfunction of endothelial cells has been valued to have a critical part in both micro and macrovascular complications of DM. Current study states that advanced glycation end products (AGEs) might also have a critical role in the enhancement of endothelial dysfunction , resulting in the long-term complications of diabetes and aging (32).

Effects of vitamin B on diabetes mellitus management are as follows:

1.4.1.1. Thiamine (Vitamin B1):

Thiamine, the coenzymatic form of vitamin B1, gets involved in two essential forms of metabolic reactions:

- ✓ decarboxylation of a-ketoacids (e.g. pyruvate, a-ketoglutarate and branched-chain keto acids)
- ✓ transketolation (e.g. among hexose and pentose phosphates).

Thiamine is essential for carbohydrate metabolism. Therefore, the dominant physiological effect of thiamin is as a co-enzyme in carbohydrate metabolism, where thiamine is needed for several levels in the disruption of glucose to supply energy. Previous phases of thiamine insufficiency may be followed with non-specific symptoms that may be neglected or easily miscomprehended. The clinical signs of sufficiency consist of anorexia; weight loss; mental alterations such as apathy, decrease in short-term memory, confusion, and irritability; muscle weakness; and cardiovascular actions such as an expanded heart (33, 34).

Cardiac impairment, muscle vulnerability, peripheral and central neuropathy are functional results of serious vitamin B1 insufficiency. Clinical expressions of beriberi (severe vitamin BI deficiency) change with age. Adults may present with dry (paralytic or nervous), wet (cardiac), or cerebral (Wernicke-Korsakoff syndrome) forms of beriberi. These conditions must be promptly treated with vitamin B1 (34). Severe vitamin B1 deficiency in

industrialized countries is likely to be related to heavy alcohol consumption with limited food consumption. In these cases renal and cardiovascular complications are life-threatening.

Thiamine has a direct action on the endocrine activity of the pancreas. For that reason, thiamine sufficiency may provide in hyperglycemia through other mechanisms rather than damaged glucose biotransformation (30). On the other hand, thiamine and its derivatives have been demonstrated to enhance endothelial action and decrease oxidative stress in unregulated glycaemic status. These mechanisms are approximately related with vascular inflammation, it could be speculate that thiamine has anti-inflammatory features (30).

In addition, it is a cofactor in the conversion of glucose to other sugars and this pathway is a major source of nicotinamide adenine dinucleotide phosphate-oxidase, required for biosynthesis of glucose and fatty acids. Diabetes might take into account a thiamine-deficient level, if not in certain terms at least close to the augmented needs assuming from accelerated and exaggerated glucose biotransformation in non-insulin dependent tissues that are predisposed to diabetic complications (35).

With the exception of its metabolic action as a coenzyme, thiamine has a role in neurotransmitter action and in nerve conduction. Anatomical alterations develop in myelinated and unmyelinated fibers, and defective nerve reconstruction provides to the pathophysiology of diabetic neuropathy. Thiamine and benfotiamine have been empirically used for the management of painful neuropathy despite questionable advantages. It may avoid nerve injury by decreasing advanced glycosylated end products (AGEs) formation in glucose-incubated cells, reducing glucose-induced apoptosis of endothelial cells and decreasing polyol accumulation by inhibition of aldose reductase expression. Enhanced endothelial function in a thiamine-rich environment has been shown by a reversal of hyperglycaemia induced reduction in endothelial cell migration and proliferation (33, 36).

Huge dose treatment with thiamine and derivative of thiamine, the thiamine monophosphate prodrug, benfotiamine (S-benzoylthiamine) are suggested as a new regimen to reverse the biochemical dysfunction leading to the progress of microvascular complications. The occurrence of high dose thiamine and benfotiamine treatment for the prevention of diabetic complications is constant with the opposite of biochemical impairment associated to the progress of diabetic complications in a consolidating action (34).

Also, latest researches demonstrate that huge dose thiamine and benfotiamine treatment is a new potential regimen for the prevention of diabetic nephropathy (37). It had been considered that thiamine intake possibly diminishes urinary albumin excretion by inverting metabolic impairment of glomerular endothelial cells, podocytes and tubular epithelial cells with relevant reduction of low-grade vascular inflammation and development of glomerular and tubular form. As a result of this structure, early-stage diabetic nephropathy may be prevented and reverted (37, 38).

It has been showed that thiamine has a valuable consequence upon various properties of the metabolic disease such as microalbuminuria, a delegate indicative of vascular risk and glycaemic control, and it could be considered that thiamine intake may have favorable outcomes upon integrally related with pathophysiological processes such as insulin resistance and hypertension.

1.4.1.2.Pyridoxine (Vitamin B6):

Vitamin B6 plays a role as a cofactor for further than 100 enzymes is included in such various mechanisms as macromolecular metabolism, immune capability, hormone activity, heme biosynthesis, and the anabolism and catabolism of sphingolipids and neurotransmitters. At the same time, it is a coenzyme that is engaged in amino acid and protein metabolism, containing aminotransferases, decarboxylases, racemases, and

dehydratases (39, 40). Therefore, causal connections between diminished vitamin B6 levels and age-related syndromes such as cardiovascular disease (CVD), Alzheimer's disease, diabetes mellitus, and cancer are reasonable (40).

The standard clinical manifestations of B6 deficiency cover:

- ✓ Skin and mucosal lesions, e.g. seborrheic dermatitis, glossitis and buccal erosions.
- ✓ Peripheral neuritis with nerve degeneration leading to sensory disturbances, polyneuropathies,
- ✓ Cerebral convulsions with electroencephalographic deformities,
- ✓ Hypochromic anaemia with microcytosis,
- ✓ Impaired lymphocyte progress and maturation, antibody preparation and T-cell action.
- ✓ Depression and confusion,
- ✓ Damaged platelet activity and clotting mechanisms (40).

The crucial unfavorable effect from huge consumption of the vitamin B6 is sensory neuropathy. In diabetic neuropathy, degenerative adjustments influence the axon first, and the myelin sheath progressively. Vitamin B derivatives affect both of these neuron constituents and promoted nerve reconstruction. Vitamin B6 is necessary for sourcing sphingosin, a structural constituent of the neural sheath (35, 41).

A huge amount of amino acid turnover is important for effective functioning of the central nervous system; a capable source of vitamin B6 is therefore needed. It shows an important role in the synthesis of biogenic amines and neurotransmitters in the brain. The change of glutamic acid to GABA (an inhibitory neurotransmitter in the central nervous system) needs vitamin B6 as a coenzyme (41).

Carpal tunnel syndrome including pain and paresthesia of the hand, is caused by irritation and compression of the medial nerve by the transverse ligaments of the wrist in ways that

are aggravated by redundant movements. These circumstances have been related with decreased flowing status of pyridoxal phosphate and diminished erythrocyte glutamic-oxaloacetic transaminase activities. It has been recommended that specific inadequacies, provoke edematous alterations to and proliferation of the synovia, leading to compression of the nerve in the carpal tunnel (42).

Various studies have demonstrated a significant relationship between increased concentrations of plasma total homocysteine and the hazard of emerging diabetic nephropathy, retinopathy, and vascular disorders, containing myocardial infarction (MI) and stroke (43). Vitamin B6 treatment has been shown to decrease the plasma concentration of homocysteine and enhance endothelial activity. Along with vitamins B12 (cobalamine) and B9 (folic acid), vitamin B6 relieves control status of homocysteine in the blood (44).

1.4.1.3. Cobalamin (Vitamin B12):

Vitamin Bl2 is a cofactor for two enzymes:

- ✓ *methionine synthase* (a reaction essential for the regeneration of tetrahydrofolic acid) : needs methylcobalamin as a cofactor for the methyl transfer from methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate.

- ✓ *L-methylmalonyl-CoA mutase:* needs adenosylcobalamin to convert L-methymalonyl-CoA to succinyl-CoA in an isomerization reaction.

In B12 inadequacy, folate may gather in the serum as a consequence of decelerating of the B12-dependent methyltransferase. A sufficient supply of B12 is needed for normal blood formation and neurological function. In addition, Vitamin B12 is a cofactor for catechol-0-methyl transferase, essential in the disruption of catecholamines, i.e. noradrenalin and dopamine in the synaptic cleft (40, 45).

The main reason of clinically noticeable cobalamin deficiency is pernicious (megaloblastic) anemia. It is a characteristic type of anemia in which enlarged cells are found. The hematological effects of cobalamin contain paleness of the skin related with a progressive onset of the common symptoms of anemia, such as diminished energy and exercise tolerance, fatigue, shortness of breath, and palpitations. The fundamental mechanism of anemia is an interference with normal deoxyribonucleic acid (DNA) synthesis. The hematological complications are completely reversed by treatment with cobalamin (45, 46).

Neurological complications are usual in individuals with clinically noticeable vitamin B12 inadequacy and contain sensory disorders in the extremities. These sensory disorders (tingling and numbness) are worse in the lower limbs. Vibratory and position sense are specifically influenced. Neurological injuries of vitamin B12 insufficiency cover diffuse and gradual nerve demyelination, illustrated as progressive neuropathy (often beginning in the peripheral nerves) and proceeding finally to the posterior and lateral columns of the spinal cord (47).

Motor disorders, containing abnormalities of walking may also emerge. Cognitive alterations may occur, ranging from deficit of concentration to memory loss, disorientation, and frank dementia, with or without state of mind changes. Moreover, visual disturbances, insomnia, sexual impotency, and damaged bowel and bladder control may occur. The advancement of neurological symptoms is changeable but mainly gradual. In case, neurological complications are reversible after treatment depends on their duration (47, 48).

On the other hand; functional cobalamin deficiency may also concluded with a disorder common in the elderly. Patients with DM is a specifically appealing nominee in this context since it is related with sensory and autonomic neuropathies very much alike to those identified in cobalamin imperfection (49). Moreover, increased homocysteine status have been associated with diabetic neuropathy, and pharmacologic doses of only

cobalamin supplementation or linked with additional vitamins may enhance peripheral and autonomic nerve activity in patients with DM. Because aging and diabetes are both related with expanded oxidative stress, a role for oxidative stress in the pathogenesis of functional cobalamin inadequacy and for the necessity of pharmacologic doses of cobalamin is suggested (49, 50).

Neuropathic pain results from the injury of peripheral nerves, and is related with hyperalgesia, casual pain and allodynia. Various clinical observations demonstrates that the administration of a mixture of thiamine, pyridoxin and cyanocobalamin is capable of decrease the painful indications of peripheral neuropathy. Huge amount of cobalamin (in cooperation with thiamine and pyridoxine) have an analgesic effect since nerve conduction velocities are enhanced (51, 52).

Vitamin B12 deficiency is a promising comorbidity that is missed, however many diabetic patients are at risk for this specific syndrome. For instance, many diabetes use metformin for their DM treatment , a drug that reduces serum vitamin B12 levels and is related with vitamin B12 inadequacy. Determining the exact aetiology of neuropathy is important since plain cobalamin substitution may invert neurologic manifestations defectively connected to hyperglycemia (53).

1.4.1.4. Folic Acid (Vitamin B9):

Folate and folic acid are arrangements of a water-soluble B vitamin. Folic acid is the more balanced type of folate placed in dietary supplements. It has only currently been widely acclaimed for its significance further its crucial efficacy in normal metabolism, especially for its pertinence to the etiologies of chronic syndromes and birth imperfections.

Folic acid has great numbers of functions, containing;

- ✓ DNA synthesis,

- ✓ red blood cell production and,
- ✓ metabolism of the amino acid methionine from homocysteine (40).

Reduced concentrations of folic acid and other B vitamins are related with raised hazard of vascular injury over homocysteine. Homocysteine has been broadly examined currently as a biomarker as well as a risk aspect for vascular disorders. It is a side product of transmethylation reactions and detoxified by methionine synthetase, which is engaged with vitamin B12 and folate as coenzymes for its appropriate activities (21,54).

Originators of hyperhomocysteinemia such as reduced concentrations of folate and vitamin B coenzymes and changed functions of enzymes drawn in the disintegration of homocysteine are also related with raised risk of cardiovascular complications (40, 55). Many researches have demonstrated that vitamins B6, B12 and folic acid inadequacies are linked with raised plasma homocysteine (56, 57). Escaled tHcy and descending levels of these vitamins that are crucial in homocysteine metabolism are indications that type 2 diabetes mellitus are at risk of recent cardiovascular occurrences. The mechanism that homocysteine boosts cardiovascular disorder is doubtful.

The unfavorable effects of HCY upon endothelial function may be interfered by diminished generation and bioavailability of nitric oxide (NO) because of oxidant stress with the production of reactive oxygen species, containing superoxide anion and hydrogen peroxide, raised lipid peroxidation and damaged production of the antioxidant glutathione peroxidase (58). In the patients with metabolic syndrome; folic acid and cobalamin therapy enhanced insulin resistance and endothelial impairment along with reducing homocysteine status. It is proposed that folic acid may have various advantageous results on cardiovascular disorder risk factors (59).

1.5. Vitamin B Consumption in Turkish Pharmaceutical Market

Both the prevalence and incidence of type 2 diabetes are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernization of lifestyle (12). Consequently, increased awareness about the effects of vitamin B treatment on diabetes mellitus management may emerge as a result of accessibility of Internet. This claim could be also proven by sales rates provided from IMS Health data.

1.5.1. IMS Health Sales Data of Supplements and Pharmaceuticals Containing Vitamin B

IMS Health is a company that supplies information, services and technology for the healthcare business. It is the biggest vendor of doctor prescribing data (60). The IMS presents a derivated projection data and is not 100 % accurate with real life sales however only 5 % deviation is considered correlated with daily market. Therefore it can be perceived as the best estimate to utilize and is valid throughout pharma industry.

Sales of supplements and pharmaceuticals containing Vitamin B derivatives are listed according to the data provided from IMS Health (Table 2).

Table 2. The IMS sales of oral & intramuscular brands containing Vitamin B in Turkish Pharmaceutical Market

	Units Year/11	Units Year/12	Units Year/13	Units Year/14
A11D4 VIT.B1+VIT.B6 &/OR B12	**11.082.447**	**11.003.013**	**10.250.473**	**9.877.179**
BENEXOL B12	5.455.443	5.907.647	5.463.370	5.166.286
APIKOBAL	2.112.775	2.585.991	2.696.388	2.834.742
NEROX B12	2.394.400	1.323.472	726.145	657.140
NOROGRIZOVIM	512.019	461.016	441.178	415.366
TRIBEKSOL	1.088	107.402	249.557	399.800
BEVITAB B12	429.105	444.884	288.844	200.917

BEFULL	0	27.987	276.465	126.392
NEUROVIT	86.740	70.667	72.018	51.359
BEVITAB	43.938	42.533	30.373	24.980
BEVITOL	37.568	26.762	5.863	197
A11F0 VITAMIN B12 PLAIN	**2.082.446**	**2.584.203**	**2.905.553**	**3.272.063**
DODEX	2.062.315	2.554.355	2.742.315	2.855.322
VITAKOBAL	0	0	127.576	371.198
SOLGAR VIT B12	19.782	26.785	29.622	34.198
VI PLEX B12	0	0	1.659	7.116
N.B.VIT B12	0	2.789	4.026	4.139
A11E1 VITAMIN B COMPLEX PLAIN	**2.402.100**	**2.224.893**	**2.305.077**	**2.319.557**
BEMIKS	1.923.889	1.790.349	1.879.482	2.031.722
BEHEPTAL	459.561	413.296	402.391	261.072
SOLGAR VIT B COMP	16.088	17.868	18.101	18.990
SOLGAR BRW.YEA.B12	2.214	3.090	4.813	6.991
A11E3 VITAMIN B COMPLEX OTHERS	**72.757**	**63.929**	**120.997**	**150.904**
NUTRIGEN UZUM	39.755	34.098	47.200	102.979
BECOZYME COMPLEX	0	1.131	51.171	38.390
PROVITAMOL	14.723	14.054	10.249	4.205
COM RINEX	11.431	6.498	5.805	2.377
ZDROVIT MVIT.MIN.	2.517	5.558	2.073	852
ZDROVIT ANT.SAMBU.	269	799	931	597
ZDROVIT MVIT.MN.WM	537	1.767	1.270	457

Routes of administration of the supplements and pharmaceuticals are demonstrated together in the table.

The take home message should be summarized as: ’B vitamins are highly preferred supportive drugs in Turkey year by year.’

1.5.2. Acquisition of Knowledge on Diabetes Mellitus (DM) Management from Google Search

Google may provide us a great deal of information in any kind of subject even within the medical scientific topics. It is recommended to have a desktop research on any topic when

it is “Googled” the phrase ‘The Importance of Vitamin B Use for the relationship between B vitamin medication and diabetes mellitus management of diabetes complications’ 6.440.000 results is obtained within 0.32 seconds (Figure 2). It is easily understood that diabetes is a very popular topic and also people are curious about any kind of treatment. One other thing is the people’s curiosity about the benefits of vitamins as there are over 6 million search results.

Figure 2. The Google Search Regarding The Importance of Vitamin B For The Management of Diabetes Mellitus

This increasingly popular citation is leaded to the conclusion that the importance is outrageously increasing with the aging population and delayed life expectancy.

2. METHOD

2.1.Aim of The Study:

The study was conducted in Istanbul Metropolitan Municipality (IMM) Darülaceze Almshouse Kayışdağı Campus were equipped to serve 1,000 people in 2012. Most of elders with chronic diseases such as diabetes were residents.The main aim of this study is to find out the effect of vitamin B use for the relationship between vitamin B supplementation and Diabetes Mellitus management in this almshouse.

2.1.1. Hypothesis:

Within the scope of main hypothesis that were shown below as 2.1., the efficacy of Vitamin B usage on Diabetes Mellitus management was observed.

(H1): Patients with diabetes use B vitamins for the prevention of diabetes complications.
H1-1: Diabetes complications have been observed less in diabetes patients using B vitamins.
H1-2: Vitamin B deficiency should be monitored in tests which performed in patients with diabetes.
H1-3: Patient satisfaction should be in correlation with hemoglobin A1c (HbA1c) values in DM management.
H1-4: A daily vitamin B supplement is appropriate for older adults.
H1-5: Patients with diabetes should use insulin injection pen / antidiabetic drugs in combination with B vitamins.
H1-6: High dose of vitamin B therapy for 3 months is a potential novel strategy for the prevention of diabetes complications.

2.2. Mixed Method:

Istanbul Metropolitan Municipality (IMM) Darülaceze Almshouse Kayışdağı Campus was equipped to serve 1,000 people in 2012. Most of elders with chronic diseases such as diabetes were residents in this almshouse. In addition, there were 11 flats and residents were segmented according to their physical & mental situation. This study was a retrospesctive study and investigated by the researcher only. It was continued from May 2012 to September 2012.

A mixed method had been used and listed as below:

- ✓ Data filtering
- ✓ Neuropathic Symptoms & General Satisfaction of Patients Assesment Form

2.2.1. Data filtering:

Istanbul Metropolitan Municipality (IMM) Darülaceze Almshouse Kayışdağı Campus had an automation system which was allowed to segment the patients as diabetics, diabetes accompanied by neuropathy and other complications. From this system it was easy to reach all biochemical test results and patient history. Data filtering process was continued from May 2012 to September 2012.

Ethical and administrative approval had been obtained from Yeditepe University Faculty of Medicine Clinical Research Committee and also Istanbul Metropolitan Municipality (IMM) Darülaceze Almshouse for the study. It was inserted as Appendix 1. Human and also patient rights were assured within this study.

The demographic values of patients were derived from automation system (age, gender, duration of diabetes, type of diabetes) to excel sheet. Diabetic patients who were already using vitamins in their current regimen were filtered. On the other hand, routes of administration of these individuals (oral or intra muscular) were detected. For participants on oral vitamins an extra coding system was added for brand names. Another data had been inserted for the duration of vitamin usage. All information regarding patient were loaded to excel and a coding system was established (Figure 3). The concomitants diseases of the subjects had also been registered to excel-based coding. Excel-based coding data analysis was inserted as Appendix 2.

There were particular reasons for selecting Istanbul Metropolitan Municipality (IMM) Darulaceze Almshouse. Reasons are shown as below:

1. The Almshouse had been serving to 1.000 residents.
2. There was an automation system operating in the Almshouse. All the lab data & medication of 1.000 individuals have been loaded to this automation system.

Weekly regular consecutive visits had been conducted to the center and relevant data were transferred from the automation system. Apart from this, residents had been visited and reviewed from all of their files to check the recent laboratory values such as HbA1c, vitamin B12 and folic acid levels. All the collected data had been processed into SPSS for statistical analysis.

SPSS program have been used. Epidemiological methods were taken into account while evaluating the data. SPSS (Statistical Package for Social Sciences) for Windows 20.0 program had used for the analysis.

The effects of vitamin B utility were checked on the course of diabetes. The aim of this was mainly focused on the effects of vitamin usage and its effects on symptoms of neuropathy, age and gender. Most of the analysis was classified in two major groups as before and after treatment. It was aimed to determine changes in the serum vitamin B12,

folate and plasma HbA1c levels of elderly patients and to investigate the relations between these parameters below:

- ✓ HbA1C Before Treatment
- ✓ HbA1C After Treatment
- ✓ Folic Acid Before Treatment
- ✓ Folic Acid After Treatment
- ✓ B12 Before Treatment
- ✓ B12 After Treatment

2.2.2. Neuropathic Symptoms & General Satisfaction of Patients Assesment Form

The aim of the assessment form was to get information about the presence of symptoms of diabetes mellitus and also overall satisfaction degree of participants. It was prepared by the researcher and conducted on all elderly with diabetes almshouse residents. The assessment form was continued from May 2012 to September 2012. Answered were replied by the patients themselves or Health Care Professional of the patient due to the mental state of them. All the answers were loaded to excel and a coding system was established.

Neuropathic Symptoms & General Satisfaction of Patients Assesment Form was inserted as Appendix 3.

3. RESULTS & DISCUSSION

The demographic characteristics of the enrolled patients and also highlights of the study were elaborated as a summary in Table 3.

Table 3. Demographic Characteristics of The Enrolled Patients and Highlights of The Study

DEMOGRAPHIC CHARACTERISTICS	**(n:110) n(%)**
Gender	
Male	63(57.3 %)
Female	47(42.7 %)
Mean Age (years)	69.24±11.64
Diabetes Type	
Type I	-
Type II	110(100)
Duration of Disease	
<10 years	94(85.5 %)
11-20 years	16(14.5 %)
21-30 years	-
>30 years	-
Concomitant Disease	
Yes	110(100 %)
No	-
Vitamin Usage	
Yes	49(44.5 %)
No	61(55.5 %)
Route of Vitamin Administration	
Oral	27(55.1 %)
IM	19(38.8 %)
Oral+IM	3(6.1 %)
Duration of Vitamin Usage (years) (n:49)	1,75±1,34

Neuropathy Symptoms	
Neuropathy +	56(50.9 %)
Neuropathy -	54(49.1 %)
Patient Satisfaction	
Excellent	-
Very Good	-
Good	71(64.5 %)
Moderate	31(28.2 %)
Not Good	8(7.3 %)
HbA_{1C} Before Treatment (n:105)	6.66±1.38
HbA_{1C} After Treatment (n:87)	6.65±1.14
Folic Acid Before Treatment (n:98)	7.77±4.11
Folic Acid After Treatment (n:71)	8.45±3.44
B12 Before Treatment (n:101)	629.83±430.41
B12 After Treatment (n:75)	623.23±365.86

A majority of participants (2/3) were males in an elderly population with mean 69 years of age. The male/female ratio could be elaborated as 57.3% male & 42.7% female (63 man – 47 woman). All of the enrolled patients (n=110) had Type 2 DM and the duration of the disease was less than 10 years in the majority of the subjects (85.5%) while 14.5 % of them had diabetes between 11-20 years. The important findings could be indicated as the duration of the disease was less than 10 years in 85.5% of the participants, while vitamin usage had been preferred almost in half of them.

- ✓ Another expected parameter was that all the individuals had concomitant disease such as cardiovascular diseases, major depression, psychotic disorder, chronic renal failure.

- ✓ Chi square analysis had been used to determine if any difference existed according to gender and vitamin usage. No statistically significant difference was found ($p=0.453$) ($p>0.05$).

- ✓ Independent Samples t test had been used in order to determine if any difference was existed according to age and vitamin usage. No statistically significant difference was observed ($p>0.05$). Vitamins were taken regularly.

- ✓ In Table 3, it was also shown that 50.9 % of participants had neuropathic symptoms. This result was compatible with the current epidemiological data.

Table 4. HbA1c, Folic Acid and B12 changes after treatment according to vitamin use and not use

	Vitamin Usage	**n**	**Mean**	**Standard Deviation**	**p Value**
HbA_{1C} After Treatment (T_1)	Used	36	6.61	1.01	**0.945**
	Not used	51	6.69	1.23	
Folic Acid After Treatment (T_2)	Used	28	7.54	3.55	**0.024***
	Not used	43	9.05	3.28	
Vitamin B12 After Treatment (T_3)	Used	30	777.86	502.23	**0.017***
	Not used	45	520.15	178.06	

*$p<0.05$ (Total T_1= 87, Total T_2= 71, Total T_3= 75)

There is no significant difference in HbA1C levels according to vitamin usage ($p>0.05$). However, significance exists in terms of B12 and folic acid designated by Mann WhitneyU test.

- Patients who had taken vitamins had higher levels of B12 values ($p<0.05$).

- Patients who had taken vitamins had lower levels of folic acid values ($p<0.05$).

It was also checked if any correlation was existed after treatment between the duration of vitamin usage and HbA1c, folic acid and vitamin B12 levels with Pearson Correlation test but could not find any statistical relevance ($p>0.05$). Average duration of vitamin usage was approximately 2 years.

On the other hand, Independent Samples t test had been used to observe if any difference existed between vitamin usage and HbA1c levels average but no difference had been detected ($p>0.05$).

Table 5. The difference between vitamin intake and Vitamin B12, Folic Acid, HbA1c values

	n	Mean	Standard Deviation	p value
HbA_{1C} Before Treatment	45	6.59	1.21	0.217
HbA_{1C} After Treatment	36	6.61	1.01	
Folic Acid Before Treatment	41	7.11	4.04	0.150
Folic Acid After Treatment	28	7.54	3.55	
Vitamin B12 Before Treatment	43	550.46	385.99	
Vitamin B12 After Treatment	30	777.86	502.22	**0.006***

***p<0.05 (n=49)**

The analysis was processed one step further and gathered results from the demographic characteristics of the patients according to vitamin usage. Wilcoxon Test had been used in order to explore the statistical differences between the evaluations before and after treatment. No significant difference has been found for HbA1c and Folic acid values ($p>0.05$). However, there was a significant increase in B12 ($p<0.05$) concentration after treatment indicating a positive streamline for the individuals. It was demonstrated at Table 5.

The main difference of data in Table 5 was lied down beneath the patient specifications. In Table 5, all the patients were using vitamins (n=49) where Table 4 segments the ones using and not using.

Table 6. Vitamin intake according to age groups

		n	Mean	Standard Deviation (SD)	p value
HbA1C Before Treatment	< 65 years old	20	6.58	1.42	
	65-75 years old	12	6.54	1.21	
	75-85 years old	11	6.64	0.92	
	> 85 years old	2	6.75	1.34	0.879
HbA1C After Treatment	< 65 years old	14	6.66	1.36	
	65-75 years old	12	6.54	0.61	
	75-85 years old	8	6.79	0.94	
	> 85 years old	2	5.90	0.71	0.576
Folic Acid Before Treatment	< 65 years old	16	7.52	4.49	
	65-75 years old	12	7.45	4.60	
	75-85 years old	10	6.25	3.23	
	> 85 years old	3	6.44	2.42	0.887
Folic Acid After Treatment	< 65 years old	11	6.75	2.65	
	65-75 years old	9	9.33	4.89	
	75-85 years old	7	6.40	2.32	
	> 85 years old	1	8.21	NA	0.447
Vitamin B12 Before Treatment	< 65 years old	17	516.24	292.86	
	65-75 years old	13	506.30	315.21	
	75-85 years old	10	623.74	574.79	
	> 85 years old	3	691.50	529.49	0.923
VitaminB12 After Treatment	< 65 years old	11	673.03	570.43	
	65-75 years old	10	1050.95	515.00	
	75-85 years old	7	564.41	277.30	
	> 85 years old	2	736.10	152.59	0.136

Although, it had been assumed just the opposite, it was found out that no significant difference had been provided for between age and HbA1c, Folic acid and B12 values ($p>0.05$) in Kruskal Wallis test. It was shown at Table 6. Regarding the data, it could be commented that, age was not a predictor for vitamin intake. No relevance was observed in any group with aging subgroups.

On the other hand, gender difference didn't play a significant role in patients' vitamin intake preference. There was no statistically significant difference between HbA1c, Folic acid and B12 values according to gender ($p>0.05$) in Mann Whitney U test.

Table 7. The route of administration of vitamins and their difference with HbA1C, folic acid and vitamin B12 levels

		n	Mean Values	Standard Deviation	p value
HbA1C After Treatment	**Oral**	18	6.25	0.60	
	Intramuscular (I.M.)	17	7.04	1.22	
	Oral+IM	1	5.80	NA	0.051
Folic Acid After Treatment	**Oral**	15	7.08	3.65	
	Intramuscular (I.M.)	12	7.63	3.21	
	oral+IM	1	13.57	NA	0.273
B12 After Treatment	**Oral**	17	881.68	551.78	
	Intramuscular (I.M.)	12	610.44	411.67	
	Oral+IM	1	1022.00	NA	0.226

Vitamin B12 deficiency is common and increases with age. Its deficiency may lead to anaemia and neurological complications. Vitamin B12 is not often prescribed in the oral form in most countries. Most people with vitamin B12 deficiency are treated in primary

care with intramuscular vitamin B12 which is an abundant source of work for health care professionals. Doctors may not be prescribing oral formulations because they are unaware of this option or have concerns regarding effectiveness. The evidence derived from limited studies proposes that huge amount oral doses of B12 (1000 mcg and 2000 mcg) could be as persuasive as intramuscular administration in achieving haematological and neurological responses (61). In line with the literature reference, the mostly preferred route of vitamin intake was oral administration (n=27, %55.1), in this study also (Table 7). Mann Whitney U test was used for this analysis, but no significance could be achieved between the route of administration of vitamins and their difference with HbA1C, folic acid and vitamin B12 levels ($p>0.05$).

Although the route of administration didn't influence HbA1c, folic acid and vitamin B12 values, it had been previously denoted that vitamin B12 value was increased after treatment at Table 5.

Table 8. Neuropathic symptoms presence and vitamin usage differences

			Vitamin Usage			
			Yes	**No**	**p value**	
Symptoms	**Neuropathy +**	n	25	24	59	
		%	44.6%	44.4%		
	Neuropathy -	n	31	30	61	
		%	55.4%	55.6%		0.983

On the other hand, values that were placed at Table 8 were derived from the data based on the questionnaire. Especially, neuropathic pain, which is one of the common symptoms of diabetic peripheral neuropathy, may be severe, have quick onset of action, and leads a decrease in quality of life, limitation of mobility, depression, and social dysfunction. Nerve

deterioration in extremities can result with pain, tingling, and loss of feeling (14). Chi square test was used to determine the relation between vitamin intake and presence of neuropathy. One could say that neuropathy was independent of vitamin usage of the patient ($p>0.05$). In addition, the relationship between route of administration of vitamin therapy and neuropathic symptoms presence was examined. Chi square test had been used to detect the difference, but no difference was observed ($p>0.05$). Similar results were found in the relationship between gender and neuropathic symptoms presence ($p>0.05$).

Table 9. Differences between neuropathic symptoms presence and age

			Age group				
			<65 years old	between 65-75 years old*	between 75-85 years old		**p value**
Symptoms	**Neuropathy +**	n	20	22	13		
		%	51.3%	68.8%	39.4%		
	Neuropathy -	n	19	10	20		
		%	48.7%	31.3%	60.6%		**0.034***

***p<0.05**

However, Chi square test had been also used to detect the relation between neuropathic symptoms and age and significant correlation was observed ($p>0.05$). It was demonstrated at Table 9. Neuropathic symptoms were seen more frequently in elderly patients between 65-75 years old. Diabetic elderly patients are at augmented risk of some type of functional degeneration concluding from diabetes complications. When natural aging process and other age-related conditions takes into account, DM may make a contribution to impoverished results in elderly people compared to those without diabetes.

Table 10. Patient satisfaction and vitamin usage difference

			Satisfaction			p value
			Good	Moderate	Not Good	
Vitamin usage	**Yes**	n	31	15	3	
		%	43.7%	48.4%	37.5%	
	No	n	40	16	5	
		%	56.3%	51.6%	62.5%	0.832

In line with the questionnaire, patient satisfaction was measured. As it was shown at Table 3, 64.5 % of the participants (n=71) responded as good, 28.2 % (n=31) admitted as moderate. However, no correlation was demonstrated between vitamin usage and patient satisfaction relationship as a result of chi square test ($p>0.05$) at Table 10. Moreover, Chi square test was used also to specify the association between gender and patient satisfaction, but no correlation presented ($p>0.05$).

Quality of life is the other crucial issue in management of elderly diabetic patients. Even though, various interferences have been discovered to extremely diminish morbidity and mortality, it is fair that the possible advantages may be related with decreased quality of life in elderly patients, especially for those with chronic situations. The potential benefits on quality of life should be considered in every treatment regimen. When the overall satisfaction results were evaluated in the study, mental state of participants should take into account. As it was shown at Table 3, 64.5 % of the participants (n=71) responded as good, 28.2 % (n=31) admitted as moderate. The main reason could be concluded as they are placed in such a good almshouse by their families or they had no relatives, which was lowered the expectations. It should be mentioned that these patients were old, had mental symptoms and stayed in a facility. Although they thought their quality of life was fairly good, it was lower compared to healthy people.

Actually, answers for the questionnaire were replied under harsh conditions. As the patients had mental symptoms sometimes, because of this situation it was required to get information from their Health Care Professionals (HCPs).

Table 11. Difference between HbA1c value and patient satisfaction

Patient Satisfaction	n	Mean HbA1c	Standard Deviation	p value
Good	59	6.71	1.11	
Moderate	23	6.60	1.32	
Bad	5	6.22	0.46	0.474

One of the important end-point of the study was to determine the patient satisfaction due to their HbA1c levels. The California Healthcare Foundation/ American Geriatric Society Panel on Improving Care for Elders with Diabetes suggested that a reasonable goal for hemoglobin A1c (HbA1c) in relatively healthy elderly with good functional status should be 7% or lower. For frail adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefits, a less stringent target of 8% was recommended (4). Kruskal Wallis test was used to determine the difference between HbA1c value and patient satisfaction, but no correlation was observed ($p>0.05$). Despite the low HbA1c levels, patient satisfaction was found good (n=59) at Table 11. The high satisfaction rates of the patients might be derived from the sanitary quality and services of the almshouse.

2.3.Limitations of the study:

There were some limitations in this study. The limitations may be indicated as below:

- ✓ The selection of one center might affect the results instead of selecting multiple centers.
    - o During the discussions with the almshouse responsible people, it was told that there were 1.000 residents and more than 60% of them were diabetics. Actually this became the reason if selecting this center however when the data was searched from the automatisation system it was found that there were only 116 diabetics. If it was known that this was the case, more centers should be added to this study.

- ✓ The elderly population in this almshouse had various concomitant diseases and took many kinds of different medication which may interact with folic acid and B12 vitamin. This situation might change their serum plasma levels presumably.

- ✓ During the first communication with the almshouse officials it was mentioned that the regular analysis of B vitamins were conducted for all the patients. However, in daily practice it was noticed that this was not the case and there was no standardisation on this issue. Unfortunately, the lab analysis were conducted sometimes within 3 months and also sometimes within 6 months intervals. Due to this, a sophisticated data couldn't be achieved on HbA1c, folic acid and vitamin B12 levels.

- ✓ The archived patient files had some deficiencies when they were reviewed in a retrospective manner.

    - For instance; the patient A's file had been filled with data until 2009 while patient B's file had data regarding 2011. The older files had been sent to a different archive of Darülaceze. The so called updated files for the residents had different time periods that change from patient to patient. It was expected that all the patient data starting from 2008 could be at the center in a standard manner however this was not the case. Data quality and statistics analysis were affected in a negative way because of this kind of inconsistencies.

No statistical significance was achieved in most of our data. This may be due to also number of sample size:

- As the study was conducted in one center.
- A powerful analysis couldn't be made and a certain target couldn't be settled for the study population.

The questionnaire was aimed to point out some major clinical features of the patient. It might be elaborated as the diabetic signs & symptoms of the patient however as some of the elderly was not capable of giving insight instead their caregivers were communicated. Cognitive impairment was an important outcome of aging which have compromized the data quality in some manner.

On the other hand, patients came from different socio–economic and intellectual levels which created a big deal of obstacle to fill the questionnaire forms accurately. The quality of information and life expectancy changes in a great variety where we suffered a lot in

data filtering process. The enrolled patients had been selected from an almshouse where we had no change to get any further information from their relatives.

The general well being and satisfaction of the patients which came out to be quite moderate to good in patients perception had been questioned. The main reason for this might be concluded as they were left in such an almshouse by their families or they have no relatives, which might lower the expectations and their quality of life.

Moreover, anemia is another consequence of vitamin B1, B6, B12 and folic acid deficiency but no regular lab tests have been standardized within these patients to point that. The difference/changes of homocycstein levels could be measured regularly as a prominent indicator of dementia.

In this study, effects of Vitamin B on diabetes mellitus (DM) management were investigated in detail. This investigation reveals current evidence is not strong enough for supplementation with vitamins to be recommended on a large scale for the prevention or management of DM. However, one very important finding of the study was the increase in vitamin B12 concentration after vitamin B supplementation. This result didn’t change with gender and different age subgroups.

3. CONCLUSION

Many elderly people have diabetes. Type 2 diabetes mellitus used to be called adult onset diabetes and occurred most frequently in middle-aged and elderly people – this is no longer the case. Many people today have Type 2 diabetes. But regardless of when its onset is, the fact remains that a growing number of elderly people have diabetes. Most people who have developed diabetic complications have been diabetic for some time. Regarding, the data it was concluded that among patients with type 2 diabetes vitamin B12 deficiency is an important factor and supplementation may be beneficial in addition to standard treatment in guidelines.

The vitamin B therapy may be an alternative and supportive treatment for the elderly but further systematical research is needed to clarify scientific evidence. One of the main problems lies down beneath the truth that most of these people have concomitant diseases and should use poly-medication. This is a main obstacle to have accurate analysis in this specific profile of patients.

Such kind of studies may be continuously conducted in this kind of centers as they have the sufficient sample size, target population and it is easy to follow them as they are perminant residents. Not only the scientific background creates a useful resource but also the quality of life of these individuals may be elevated.

Actually, if such a clinical study could be initiated nationally one can derive comprehensive epidemiologic data. More highquality, double-blind randomized controlled trials are needed to confirm the clinical effectiveness of vitamin B usage on diabetes mellitus management. Further research should be conducted in multicenter approach with sufficient number of patients to get more accurate clinical results.

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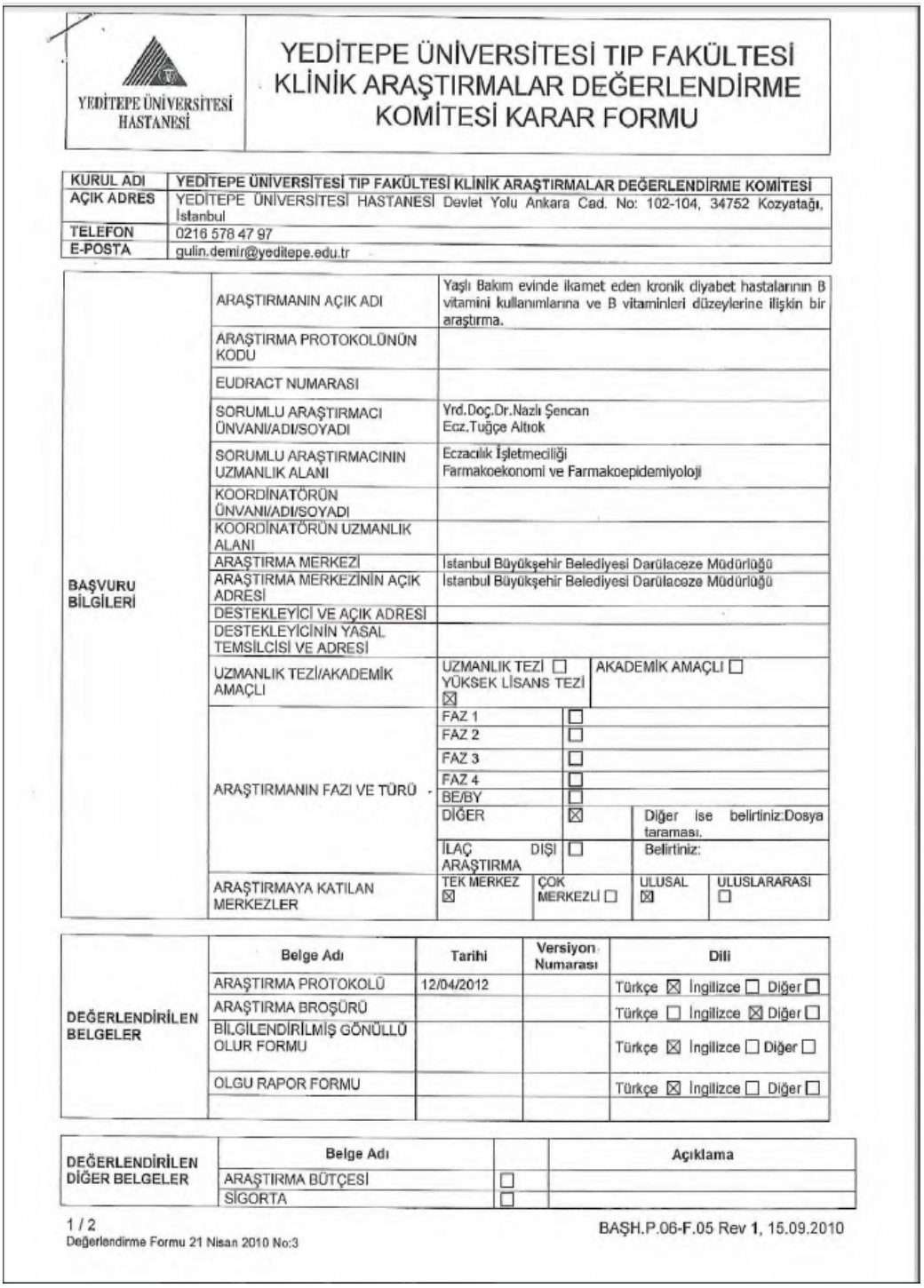
5. APPENDICES

5.1. Appendix 1: The Ethical Approval Form

5.2. Appendix 2: The Excel Based Coding Data Analysis

5.3. Appendix 3: Neuropathic Symptoms & General Satisfaction of Patients Assesment Form

6.1. Appendix 1: The Ethical Approval Form



YEDİTEPE ÜNİVERSİTESİ HASTANESİ

YEDİTEPE ÜNİVERSİTESİ TIP FAKÜLTESİ KLİNİK ARAŞTIRMALAR DEĞERLENDİRME KOMİTESİ KARAR FORMU

KURUL ADI	YEDİTEPE ÜNİVERSİTESİ TIP FAKÜLTESİ KLİNİK ARAŞTIRMALAR DEĞERLENDİRME KOMİTESİ
AÇIK ADRES	YEDİTEPE ÜNİVERSİTESİ HASTANESİ Devlet Yolu Ankara Cad. No: 102-104, 34752 Kozyatağı, İstanbul
TELEFON	0216 578 47 97
E-POSTA	gulin.demir@yeditepe.edu.tr

BAŞVURU BİLGİLERİ	ARAŞTIRMANIN AÇIK ADI	Yaşlı Bakım evinde ikamet eden kronik diyabet hastalarının B vitamini kullanımlarına ve B vitaminleri düzeylerine ilişkin bir araştırma.
	ARAŞTIRMA PROTOKOLÜNÜN KODU	
	EUDRACT NUMARASI	
	SORUMLU ARAŞTIRMACI ÜNVANI/ADI/SOYADI	Yrd.Doç.Dr.Nazlı Şencan Ecz.Tuğçe Altıok
	SORUMLU ARAŞTIRMACININ UZMANLIK ALANI	Eczacılık İşletmeciliği Farmakoekonomi ve Farmakoepidemiyoloji
	KOORDİNATÖRÜN ÜNVANI/ADI/SOYADI	
	KOORDİNATÖRÜN UZMANLIK ALANI	
	ARAŞTIRMA MERKEZİ	İstanbul Büyükşehir Belediyesi Darülaceze Müdürlüğü
	ARAŞTIRMA MERKEZİNİN AÇIK ADRESİ	İstanbul Büyükşehir Belediyesi Darülaceze Müdürlüğü
	DESTEKLEYİCİ VE AÇIK ADRESİ	
	DESTEKLEYİCİNİN YASAL TEMSİLCİSİ VE ADRESİ	
	UZMANLIK TEZİ/AKADEMİK AMAÇLI	UZMANLIK TEZİ ☐ YÜKSEK LİSANS TEZİ ☒ / AKADEMİK AMAÇLI ☐
	ARAŞTIRMANIN FAZI VE TÜRÜ	FAZ 1 ☐ FAZ 2 ☐ FAZ 3 ☐ FAZ 4 ☐ BE/BY ☐ DİĞER ☒ Diğer ise belirtiniz:Dosya taraması. İLAÇ DIŞI ARAŞTIRMA ☐ Belirtiniz:
	ARAŞTIRMAYA KATILAN MERKEZLER	TEK MERKEZ ☒ / ÇOK MERKEZLİ ☐ / ULUSAL ☒ / ULUSLARARASI ☐

DEĞERLENDİRİLEN BELGELER	Belge Adı	Tarihi	Versiyon Numarası	Dili
	ARAŞTIRMA PROTOKOLÜ	12/04/2012		Türkçe ☒ İngilizce ☐ Diğer ☐
	ARAŞTIRMA BROŞÜRÜ			Türkçe ☐ İngilizce ☒ Diğer ☐
	BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU			Türkçe ☒ İngilizce ☐ Diğer ☐
	OLGU RAPOR FORMU			Türkçe ☒ İngilizce ☐ Diğer ☐

DEĞERLENDİRİLEN DİĞER BELGELER	Belge Adı		Açıklama
	ARAŞTIRMA BÜTÇESİ	☐	
	SİGORTA	☐	

1 / 2
Değerlendirme Formu 21 Nisan 2010 No:3

BAŞH.P.06-F.05 Rev 1, 15.09.2010

YEDİTEPE ÜNİVERSİTESİ HASTANESİ

YEDİTEPE ÜNİVERSİTESİ TIP FAKÜLTESİ KLİNİK ARAŞTIRMALAR DEĞERLENDİRME KOMİTESİ KARAR FORMU

	HASTA KARTI/GÜNLÜKLERİ	☐	
	İLAN	☐	
	YILLIK BİLDİRİM	☐	
	SONUÇ RAPORU	☐	
	GÜVENLİLİK BİLDİRİMLERİ	☐	
	DİĞER	☐	

KARAR BİLGİLERİ	Karar No: 183	Tarih:08/05/2012
	Yrd.Doç.Dr.Nazlı Şencan,Ecz.Tuğçe Altıok sorumluluğunda yapılması tasarlanan ve yukarıda başvuru bilgileri verilen klinik araştırma başvuru dosyası ve ilgili belgeler araştırmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş, gerçekleştirilmesinde etik bir sakınca bulunmadığına toplantıya katılan değerlendirme kurulu üyelerinin oy çokluğu ile karar verilmiştir.	

DEĞERLENDİRME KOMİTESİ BİLGİLERİ

ÇALIŞMA ESASI	Klinik Araştırmalar Hakkında Yönetmelik, İyi Klinik Uygulamaları Kılavuzu, Yeditepe Üniversitesi Tıp Fakültesi, Klinik Araştırmalar Değerlendirme Komitesi Kuruluş ve Çalışma Esasları.

DEĞERLENDİRME KURUL BAŞKANI UNVANI/ADI/SOYADI: Prof. Dr. R. Serdar ALPAN

DEĞERLENDİRME KOMİTESİ ÜYELERİ

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Cinsiyet		İlişki *		Katılım **		İmza
Prof. Dr. R. Serdar Alpan	Farmakoloji	YÜTF	E ☒	K ☐	E ☐	H ☒*	E ☒	H ☐	
Prof. Dr. M. Reha Cengizlier	Pediatri	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. S. Sami Kartı	Hematoloji	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Serdar Öztezcan	Biyokimya	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Yrd. Doç. Dr. Baki Ekçi	Genel Cerrahi	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Doç Dr. Ferda Özkan	Patoloji	YÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Nural Bekiroğlu	Biyoistatistik	MÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Doç. Dr. Esra Can Say	Diş Has. Ted.	YÜDF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Doç. Dr. Meriç Köksal	Eczacılık	YÜEF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Ali Rıza Okur	Hukuk	YÜHF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Doç. Dr. Başar Atalay	Beyin Cerrahi	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Yrd.Doç.Dr.Nesrin Sarıman	Göğüs Hastalıkları	MÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Yrd.Doç.Dr.Esin Öztürk Işık	Biyomedikal Mühendisi	YÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Bilge Firuzbay	Sivil Üye/Emekli		E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	

* : Araştırma ile İlişki
** : Toplantıda Bulunma

Önemli Not: Çalışmanızın Klinik Araştırmalar Değerlendirme Komitesi tarafından onaylanan protokole göre yürütülmesi ve çalışma protokolündeki değişikliklerin kurulumuza bildirilmesi gerekmektedir.

6.2. Appendix 2: The Excel Based Coding Data Analysis

This data analysis was prepared by using of the automation system of Istanbul Metropolitan Municipality (IMM) Darülaceze Almshouse Kayışdağı Campus.

1. Patient's name: Written as is.

2. The name of the related site: Written as is.

- ✓ Site 1: Çınar flat
- ✓ Site 2: Umut flat
- ✓ Site 3: Dr. Beşir Akınal flat
- ✓ Site 4: Hayat flat
- ✓ Site 5: Papatya flat
- ✓ Site 6: Dolunay flat
- ✓ Site 7: Güven flat
- ✓ Site 8: Sevgi flat
- ✓ Site 9: Huzur flat
- ✓ Site 10: Zümrüt flat
- ✓ Site 11: Pocket Darülaceze flat

3. Birth date: Written as is.

4. Duration of stay: Written as is.

5. Gender

- ✓ Woman: 1
- ✓ Men: 2

6. Type of Diabetes:

- ✓ Type I: 1
- ✓ Type II: 2

7. The time of first diagnosis of Diabetes:

- ✓ Less than 10 years: 1
- ✓ Between 11-20 years: 2
- ✓ Between 21-30 years: 3
- ✓ More than 30 years: 4

8. Is there any concomitant chronic disease beside Diabetes?

- ✓ If exists: 1
- ✓ If does not exist: 2

9. Which of the chronic diseases do they have as stated below?

- ✓ Cardiovascular Disease: 1
- ✓ Chronic Bronchitis / Chronic Obstructive Pulmonary Disease: 2
- ✓ Thyroid Dysfunctions: 3
- ✓ Alzheimer Disease: 4
- ✓ Major Depression / Psychotic Disorder: 5
- ✓ Vertigo: 6
- ✓ Epilepsy: 7
- ✓ Gastrointestinal Disease: 8
- ✓ Behçet‘s Syndrome: 9
- ✓ Chronic Renal Failure : 10
- ✓ Eye Diseases (Xerophtalmia / Glaucoma / High Eye Pressure) :11
- ✓ Osteoporosis: 12
- ✓ Parkinson Disease:13
- ✓ Hemiplegia: 14
- ✓ Bipolar Disorder/ Schizophrenia: 15
- ✓ Mental Retardation: 16
- ✓ Spasticity: 17
- ✓ Benign Prostatic Hyperplasia / Incontinence: 18
- ✓ Osteo / Rheumatoid Arthritis: 19
- ✓ Prostate Disease: 20

- ✓ Chronic Liver Disease: 21
- ✓ Chronic Sinus: 22
- ✓ Cancer:23
- ✓ Chronic gingivitis: 24

10. Are there any other regular vitamin supplementation that they take?

- ✓ If exists: 1
- ✓ If does not exist: 2

11. What is/are the route of administration of vitamin B supplements?

- ✓ Oral: 1
- ✓ Intramuscular: 2
- ✓ Oral + Intramuscular: 3

12. What are the name of brands of vitamin B supplements that they take?

BRAND NAMES OF ORAL PREPARATIONS:

- ✓ Benexol B12 Tablet: 11
- ✓ Nerox B12 Tablet : 12
- ✓ Neuvitab Tablet: 13
- ✓ Apikobal Tablet: 14
- ✓ Bevitab-B12 Tablet: 15
- ✓ Tribeksol Tablet: 16
- ✓ Bitavin-B12 Tablet: 17
- ✓ Bemiks Tablet: 18
- ✓ Folbiol Tablet: 19
- ✓ Supradyn Sugar-coated Pill: 20
- ✓ Neuvitan Tablet: 23

BRAND NAMES OF INJECTABLE PREPARATIONS:

- ✓ Dodex Ampoule: 21
- ✓ Cernevit Ampoule: 22

BRAND NAMES OF BOTH ORAL & INJECTABLE PREPARATIONS

- ✓ Dodex Ampoule+ Nerox B12 Tablet: 23
- ✓ Benexol B12 Tablet + Folbiol Tablet: 24
- ✓ Folbiol Tablet + Dodex Ampoule: 25
- ✓ Benexol B12 Tablet + Dodex Ampoule: 26

13. Duration of vitamin B supplement usage: Written in terms of years.

14. Symptoms of the Diabetic Patients

(Answers were based and evaluated on the questionnaire results):

Answered by Health Care Professional of the each patient.

- ✓ Patients with symptoms related neuropathy: 1 + 4 + 5 + 7= 1
- ✓ Patients with no symptoms related neuropathy: 2 + 3 + 6 = 2

a. Pain/ Insensibility / Sensory loss of hands and arms / Tingling / Numbness / Sensitivity to heat or contact → 1

b. Visual problems (blurred vision, small dots/lines, reduced night vision, loss of accommodation reflex, loss of vision etc.) → 2

c. Frequent nocturnal urination/ Fatigue / Tachycardia / Reduction in daily urine/ Edema in hands & feet → 3

- ✓ a + b → 4
- ✓ a + c → 5
- ✓ b + c → 6
- ✓ a + b + c → 7

15. Overall satisfaction rate of the patient:

(Answers were based and evaluated on the questionnaire results):

Answered by Health Care Professional of the each patient.

- ✓ Excellent: 1
- ✓ Very Good: 2
- ✓ Good: 3
- ✓ Moderate: 4
- ✓ Not Good: 5

6.3. Appendix 3: Neuropathic Symptoms & General Satisfaction of Patients Assesment Form

Answer every question by placing a check mark on the line in front of the appropriate answer. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. Which of the following syptoms do you have due to your Diabet Mellitus (DM) disease?

- ☐ Sensory loss of hands and arms
- ☐ Tingling
- ☐ Pain in Extremities
- ☐ Sensitivity to heat or contact
- ☐ Visual problems (blurred vision, small dots/lines, reduced night vision, loss of accommodation reflex)
- ☐ Frequent nocturnal urination
- ☐ Fatigue
- ☐ Tachycardia
- ☐ Reduction in daily urine
- ☐ Edema in hands & feet

2. Could you please rate the overall satisfaction degree for your health status due to vitamin usage?

- ☐ Excellent
- ☐ Very Good
- ☐ Good
- ☐ Moderate
- ☐ Not Good

Figure 3. A Detailed Screenshot From Excel-Based Coding Data Analysis

The name of the related site	Birth Date	Duration of stay	Gender	Type of Diabe	The time of first diagnosis of Diabete	Concomitant Chronic Disease	Which Chronic Diseases	Vitamin Usage?
8	1956	12.09.2006	2	2	1	1	1,2,6,7,8,9	2
9	1948	29.04.2009	2	2	1	1	1,3	1
10	1950	10.10.2008	2	2	1	1	1,8,2	1
8	1938	31.12.2007	2	2	1	1	1,8	1
9	1952	10.07.2007	2	2	1	1	1,8,14	1
8	1942	11.01.2011	2	2	1	1	4,1,5	1
9	1936	12.11.2010	2	2	1	1	8,1,4,2	2
7	1954	03.12.2009	1	2	1	1	3,1,10,12,8	2
9	1930	01.06.2011	1	2	2	1	2,1,8,5,3	2
5	1958	12.03.2001	1	2	2	1	5,1,16,8	2
9	1943	07.02.2002	2	2	1	1	1,19,5,8	2
8	1935	11.09.2006	2	2	1	1	1,5,8,13,4	2
7	1942	07.04.2010	1	2	1	1	1,5,8,12,7	1
3	1928	06.12.2006	2	2	2	1	1,20,3	2
8	1948	22.03.2004	2	2	1	1	15,1,4,8,18	2
6	1955	01.11.2011	2	2	1	1	15,13,5,2,7,1	1
9	1939	05.05.2006	1	2	1	1	18,1,3,5,8	1
9	1946	23.01.2007	2	2	1	1	1,5,14	2
7	1951	12.03.2001	1	2	2	1	1,13,8,5,18,7	2
5	1956	13.01.2004	1	2	1	1	15,8	1
9	1964	10.09.2003	2	2	1	1	18,5,1,8	1
6	1948	01.11.2001	2	2	1	1	1,5	2
7	1934	29.06.2001	1	2	1	1	1,2,6,11,8,5	2

6. CURRICULUM VITAE

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2004 - 2005 : Yeditepe University, Faculty of Engineering and Architecture, Chemical Engineering, Istanbul / TURKEY (Transfer)

2004 - Present : Anadolu University, Faculty of Economics and Administrative Sciences, Business Administration, as 2nd university, Istanbul / TURKEY

1996 - 2003 : Nişantaşı Anatolian High School, Istanbul, TURKEY

EXPERIENCE

Bayer Turk, Consumer Care Medical Advisor, Istanbul	05.2013 - Present
Bayer Turk, Consumer Care Medical Scientific Liaison, Istanbul	12.2009 - 05.2013
Bayer Turk, Medical Management Trainee, Istanbul	08.2009 - 12.2009
Sanofi-aventis Pharmaceuticals Ltd.Şti., Regulatory Affairs Intern, Istanbul	08.2008 - 06.2009
Bakırköy Acıbadem Hospital, Istanbul	06.2008 - 08.2008
Akmerkez Pharmacy, Istanbul	08.2007 - 09.2007
Yeditepe University, Faculty of Pharmacy, Istanbul	2006 - 2007