# The relation of vascular complications to carotid intima-media thickness in patients with type II diabetes mellitus

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*Microvascular and macrovascular complications are the most important causes of the mortality and morbidity in patients with diabetes mellitus. Atherosclerosis is the main mechanism in the genesis of those complications. The diabetes itself causes a risk for atherosclerosis and diabetics may also own a high incidence of other risk factors for atherosclerosis. Thickening of the intima-media complex in great vessels is the first morphologic feature of the atherosclerosis. Thickness of the carotid intima-media serves as an indicator of the carotid atherosclerosis. On the other hand, it gives an useful information about atherosclerotic course at the other regions, too. We evaluated common carotid arteries, because aorta and its branches are the first region which are affected by atherosclerosis and it can be examined easily and non-invasively by B-mode ultrasonography. In this study, we investigated the relation of the vascular complications to the thickness of the carotid intima-media complex in 79 non-insulin-dependent diabetics. We established that the thickness of the carotid intima-media complex increases with the existence and the number of vascular complications. In conclusion, the thickness of the carotid intima-media complex can be claimed as a parameter of the atherosclerotic status of diabetics. So, we may recommend that carotid ultrasonography should be performed routinely in all diabetics. [Turk J Med Res 1997; 15(2):72-76]*

**Key Words:** Diabetes mellitus, Diabet complications. Atherosclerosis, Carotid artery intima-media thickness

Diabetes mellitus is a heterogeneous primary disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. Non-insulin-dependent diabetes mellitus (NIDDM) may be the most rapidly growing chronic disease in the world. Its long-term complications, including retinopathy, nephropathy, neuropathy, and accelerated macrovascular disease causes major morbidity and mortality. Atherosclerosis is the main mechanism in the genesis of the microvascular and macrovascular complications. The diabetes itself causes a risk for atherosclerosis and diabetics may also own a high incidence of other risk factors for atherosclerosis.

Nonenzymatic glycosilation of the proteins play an important role in the genesis of macrovascular complications. Other factors, such as increased oxidative modification of the lipoproteins, dyslipidemia and hyperinsulinemia also can facilitate the development of the macrovascular complications (1-3).

Diabetic macrovascular complications occur gradually and insidiously during course of the disease, and they can be described as accelerated atherosclerotic events. Myocardial infarction, cerebrovascular events or peripheral arterial occlusions in the range of claudication to lower extremity amputation, all of are undesirable outcomes of macrovascular disease (4). Retinopathy, nephropathy and neuropathy which develop due to microvascular complications, are also causes of the increased morbidity and mortality (5,6).

Because of the aorta and its branches are the first regions affecting from atherosclerosis, thickness of the carotid intima-media is a good indicator for atherosclerotic progression. Thus, thickness of the carotid intima-media is also gives useful information about atherosclerotic course of the other regions (7).

The purpose of our study is to determine the relation of vascular complications to carotid intima-media thickness (IMT) and to establish whether the IMT is an useful parameter for evaluating peripheral vascular disease or not.

## MATERIAL AND METHODS

This study was carried out between October 1995 and July 1996, and included 79 patients with non-insulin dependent diabetes mellitus (NIDDM). Patients whose fasting blood glucose higher than 140 mg/dl were accepted as diabetic. Those patients have been treated either by oral antidiabetic drugs or insulin. Diabetic patients were accepted as NIDDM according to these criteria:

1- Onset of symptoms after age 30.

2- Positive family history of diabetes mellitus.

3- Clinical background of onset of diabetes.

**Received:** Dec. 14, 1996 **Accepted:** April 1, 1997

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Patients who were receiving hypolipidemic drugs or calcium channel blockers were excluded from our study.

Carotid ultrasonography (CUS) were performed to all patients with Acuson 128 XP *15* US, before determination of clinical risk factors and complications. Carotid artery was visualised both in transverse and longitudinal planes. In images made in the longitudinal plane, the intima-media complex was seen as a hyperechogenic line separated by the pair of parallel echogenic lines. Distance between the hyperechogenic lines measured as the IMT. Measurements were done from far-wall of common carotid and 2 cm proximal to bulb. Three measurements (anterolateral, lateral and posterolateral) were done for each common carotid artery, and mean of these values accepted as IMT.

Following CUS, all patients were examined for retinopathy, neuropathy, nephropathy, peripheral artery disease (PAD) and ischaemic heart disease (IHD) which are diabetic complications. Retinopathy was evaluated by experienced ophthalmologist with standard ophthalmological and fundoscopic examination. Neuropathy was detected by medical history and physical examination. 24-hour urine was analysed for proteinuria in all patients to establish the nephropathy. Ischaemic heart disease was detected basing on history of chest pain, myocardial infarction and/or previous angiography and electrocardiography findings. History of claudication and positive findings in peripheral arterial examination where accepted as evidence of peripheral artery disease.

## Definition of diabetic complications and classify of patients

Retinopathy: Patients were divided into three groups as without retinopathy, with background retinopathy and with proliferative retinopathy. Diabetic background retinopathy was described with the presence of venous abnormalities, microaneurysms, retinal haemorrhages, retinal edema and exudates. The findings of neovascularization, glial proliferation, vitreoretinal traction, retinal detachment and haemorrhage into the vitreus were determined proliferative retinopathy. Patients who had been given photocoagulation therapy were also accepted as proliferative retinopathy.

Neuropathy: Neuropathy was determined with the history of numbness, tingling, pins-and-needles sensation and the findings of weak or lost deep tendon reflexes, hypoesthesia or weakness. Patients were divided into two groups by presence and absence of neuropathy.

Nephropathy: Patients were divided into two groups by the amount of the proteinuria, such as higher than the 200 mg and lower than the 200 mg per 24-hour.

Ischaemic heart disease: IHD was detected basing on history of chest pain, myocardial infarction and/or previous angiography and electrocardiography findings. Two patient groups were constituted, with IDH and without IHD.

Peripheral artery disease: The presence of claudication history and pulse defects on arterial examination were accepted as PAD and, two groups determined as patients with PAD and without PAD.

All patients were divided into two main groups as patients with complications and without complications according to criteria described above. The presence of at least one complication was accepted as adequate to participate to complication group. The patients were also classified according to number of complications.

The data was processed by computer using SPSS (Statistical Program for the Social Sciences, Release 6.00). Stem-and-leaf plot was used for the normal probability analysis. Results were compared by using a two-sample t-test, variance analysis and Mann-Whitney U test.

## RESULTS

Patient group consisted of 47 females (mean age 64.4± 9.5 years (range 48 to 88) and 32 males (mean age 59.7±6.8 years (range 48 to 70). The mean age of the all patients were 62.5 ± 8.8 years (range 48 to 88).

Sixty-eight percent of patients were at the age of 55 to 74 years old. 74.7% were non-smoker. Cholesterol level was higher than 200 mg/dl in 57% and triglyceride level higher than 150 mg/dl in 50.6%. BMI was within the range of 25 to 30 kg/m$^2$ in 45.6%. Systolic blood pressure was within normal ranges in 48.1% and diastolic blood pressure was within normal ranges in 65.8%. Duration of diabetes was longer than 15 years in 32.9% of patients.

The distribution of patients according to detected complications was presented in Table 1.

**Table 1,** The distribution of patients according to detected complications

| Complications | Number of patient (n) | % |
|---|---|---|
| With complication | 50 | 63.3 |
| Without complication | 29 | 36.7 |
| **Retinopathy** | | |
| Proliferative | 12 | 15.2 |
| Background retinopathy | 30 | 38.0 |
| Without retinopathy | 37 | 46.8 |
| **Neuropathy** | | |
| Present | 38 | 48.1 |
| Absent | 41 | 51.9 |
| **Nephropathy** | | |
| Present | 20 | 25.3 |
| Absent | 59 | 74.7 |
| **Ischaemic heart disease** | | |
| Present | 30 | 38.0 |
| Absent | 49 | 62.0 |
| **Peripheral artery disease** | | |
| Present | 10 | 12.7 |
| Absent | 69 | 87.3 |
| **Number of complication** | | |
| One | 8 | 10.1 |
| Two | 12 | 15.2 |
| Three | 18 | 22.8 |
| Four | *m* i | 7.6 |
| Five | 6 | 7.6 |

**Table 2.** Mean IMTs of left and right common carotid arteries according to presence or absence of complication

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| Complication | Mean + SD | t | P | Mean + SD | t | P |
| Present | 0.82 + 0.12 | | | 0.85 + 0.11 | | |
| Absent | 0.62 + 0.08 | -8.75 | <0.05 | 0.64 + 0.05 | -11.3 | <0.05 |

**Table 3.** The number of complications and mean IMT values

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| Number of complication | Mean + SD | Khi-square | P | Mean + SD | Khi-square | P |
| 0 | 0.62 + 0.08 | | | 0.64 + 0.05 | | |
| 1 | 0.69 + 0.08 | | | 0.73 + 0.09 | | |
| 2 | 0.78 + 0.07 | | | 0.77 + 0.07 | | |
| 3 | 0.83 + 0.10 | | | 0.87 + 0.09 | | |
| 4 | 0.90 + 0.03 | | | 0.91+0.04 | | |
| 5 | 0.93 + 0.17 | 48.58 | <0.05 | 1.00 + 0.03 | 61.23 | <0.05 |

Sixty-three percent of patients have at least one complication or more. The most commonly seen complication was retinopathy (53.2%) and, the least was peripheral artery disease (12.7%).

Mean IMT of left and right common carotid arteries according to presence or absence of complication are shown in Table 2.

As shown in Table 3, both left and right IMT values were increased with parallel to number of complication, differences were statistically significant ($p<0.05$ and $p<0.05$). Figure 1 shows this result, the lines pointing IMT values upward related to number of complication.

Mean IMT of left and right common carotid arteries according to presence or absence of retinopathy, neuropathy, nephropathy, IDH and PAD were shown in tables 4,5,6,7 and 8 respectively.

The differences between the mean IMT of left and right common carotid arteries and retinopathy, neuropathy, nephropathy, IDH and PAD were statistically significant ($p<0.05$)

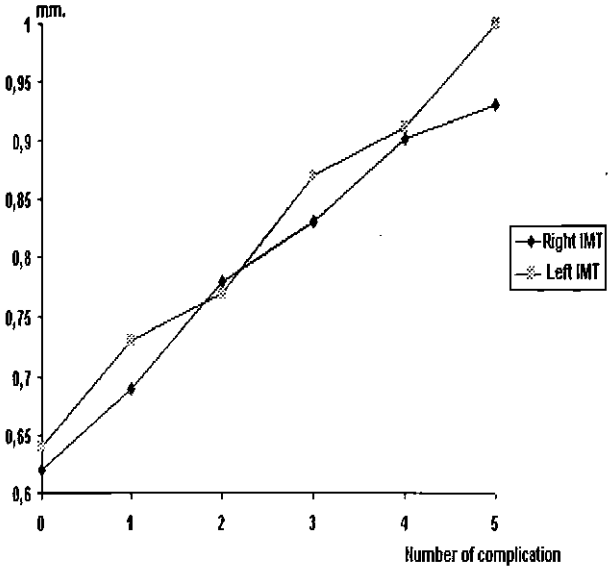


**Figure** 1. The relation of number of complication to mean IMT values.

## DISCUSSION

Since the microvascular complications such as retinopathy or neuropathy are responsible for morbidity, the macrovascular complications play the most important role in the increment of mortality in diabetic patients. Macrovascular complications can be described as an accelerated atherosclerosis. Thickness of the intima-media complex in large vessels is the first evidence of atherosclerosis. Thus, measurement of IMT is a useful method

**Table 4.** Mean IMT of left and right common carotid arteries according to retinopathy

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| Retinopathy | Mean + SD | Khi-square | P | Mean + SD | Khi-square | P |
| Proliferative | 0.89 + 0.10 | | | 0.94 + 0.09 | | |
| Background | 0.80 + 0.07 | | | 0.82 + 0.09 | | |
| Absent | 0.66 + 0.13 | 25.99 | < 0.05 | 0.67 + 0.11 | 42.28 | <0.05 |

**Table 5.** Mean IMT of left and right common carotid arteries according to neuropathy

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| Neuropathy | Mean + SD | t | p | Mean + SD | t | p |
| Present | 0.84 + 0.11 | | | 0.87 + 0.11 | | |
| Absent | 0.65 + 0.09 | -8.24 | < 0.05 | 0.68 + 0.09 | -8.86 | < 0.05 |

**Table 6.** Mean IMT of left and right common carotid arteries according to nephropathy

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| Nephropathy | Mean + SD | t | p | Mean + SD | t | p |
| Present | 0.90 + 0.11 | | | 0.93 + 0.07 | | |
| Absent | 0.69 + 0.11 | -7.54 | < 0.05 | 0.71+0.11 | -8.94 | < 0.05 |

**Table 7.** Mean IMT of left and right common carotid arteries according to IHD

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| IHD | Mean + SD | t | p | Mean + SD | t | p |
| Present | 0.83 + 0.14 | | | 0.88 + 0.12 | | |
| Absent | 0.69 + 0.11 | -4.74 | < 0.05 | 0.71 +0.11 | -6.56 | < 0.05 |

**Table 8.** Mean IMT of left and right common carotid arteries according to PAD

| | IMT of right common carotid | | | IMT of left common carotid | | |
|---|---|---|---|---|---|---|
| PAD | Mean + SD | t | p | Mean + SD | , \ | p |
| Present | 0.86 + 0.12 | | | 0.82 | | |
| Absent | 0.73 + 0.13 | -4.42 | < 0.05 | 0.75 | -5.12 | <0.05 |

to establish the atherosclerosis at subclinical stages. This measurement can be performed easily from common carotids by using B mode US.

The correlation between atherosclerotic risk factors and carotid IMT had been widely examined, but the presence or the number of micro-macrovascular complications and carotid IMT had not been examined before. So, we have designed this study.

In our study, we found that common carotid IMT increases parallel to presence and number of macro and microvascular diabetic complications such as retinopathy, neuropathy, nephropathy, IDH and PAD.

Coronary atherosclerosis is the most common cause of mortality in the diabetic patients. It has been established that the incidence of IHD increases with the thickness of the carotid intima-media complex (9). Of course the atherosclerotic risk factors influence both the coronary arteries and carotids. Atherosclerosis of the coronary arteries and carotid arteries had been observed with together on autopsy studies (10).

We could not find any paper related to correlation between carotid IMT and diabetic vascular complications in NIDDM. In some studies about IDDM, retinopathy had been found as closely related to increased carotid IMT, this result suggested that micro and macrovascular complications occur together (6). Our findings were concordant with this result, the whole of micro and macrovascular complications were increasing parallel to carotid IMT.

Proteinuria in patients with NIDDM almost always was accompanied with hypertension. Lipid abnormalities due to nephropathy and hypertension lead to acceleration of atherosclerosis. That means increased IHD and increased mortality (5). In our study, IMT values were significantly higher in patients with proteinuria (due to diabetic nephropathy) than without proteinuria. The same relationships were also determined between neuropathy, retinopathy and increased carotid IMT. IMT values were higher in patients with proliferative retinopathy than background retinopathy.

As in microvascular complications described above, macrovascular complications such as IHD and PAD, were also found increased in number and severity related to IMT. Carotid IMT values were significantly higher in patients with IHD. Evaluation of carotids by using B mode US may be useful to establish the atherosclerotic status, since, the silent myocardial ischaemia is common in diabetic patients

In conclusion, the thickness of the carotid intima-media complex increases with the presence and number of microvascular and macrovascular complications. The measurement of carotid IMT can be claimed as a parameter that can specify the atherosclerotic status of diabetics. So.we may recommend that carotid ultrasonography should be performed routinely in all diabetics.

**Tip II diabètes mellitusta kan basıncı ve serum lipidleri ile karotis intima-media kalınlığı arasındaki ilişki**

*Diabetli hastalarda mortalité ve morbiditenin en önemli nedeni mikro ve makrovasküler komplikasyonlardır. Bu vasküler komplikasyonların gelişmesinde temel mekanizma ateroskleroz dur. Diabetik kişilerde hem diabetin kendisi bir ateroskleroz risk faktörüdür, hem de diabetiklerde aterosklerozun diğer risk faktörleri daha sık görülmektedir. Büyük damarlarda intima-media kompleksinin kalınlaşması aterosklerozun ilk morfolojik belirtisidir. Karotis intima-media kalınlığı hem karotis aterosklerozu için bir gösterge, hem de diğer bölgelerdeki ateroskleroz için bir habercidir. Çalışmamızda karotis arterinin seçilmesinin nedeni ateroskleroza ilk tutulan damarların aort ve dalları olması ve bu arterin B mod US ile kolayca ve non-invaziv bir şekilde görüntülenebilmesidir. Çalışmamızda, 79 NIDDM'li hastada ateroskleroz risk faktörleri ve vasküler komplikasyonlar ile karotis intima-media kalınlığı arasındaki ilişkiyi inceledik. Karotis İMK'nın hastaların sistolik kan basıncı ve hipertrigliseridemi ile arttığını oysa diastolik kan basıncı ve kolesterol düzeyi ile farklılık göstermediğini tesbit ettik. Bu sonuçlara göre, karotis İMK diabetik kişilerde kişinin ateroskleroz açısından durumunu belirlemede kullanılabilir bir parametredir ve bu sonuçlarla biz tüm diabetiklere rutin olarak karotis US yapılmasını öneriyoruz.*
*[T Klin Araştırma 1997; 15(2):72-76]*

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