# Evaluation of Cerebral Vasoreactivity in Type2 Diabetic Patients by using Transcranial Doppler Ultrasonography (TCD)

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# **Abstract**

**Background** Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular and cerebrovascular diseases with high mortality and disability. Cerebral vasomotor reactivity (VMR), one of the most accurate markers of cerebral hemodynamics, has been shown to be impaired in subjects with carotid artery steno-occlusive disease and associated with an increased risk of ischemic events. Transcranial Doppler ultrasonography (TCD) study have been used to investigate cerebral vasoreactivity to identify patients with increased risk and to better plan the treatment.

**Objective:** The aim of study was to assess cerebral vasoreactivity among type2 diabetes mellitus patients by using transcranial Doppler ultrasonography.

**Patients and method:** sixty five persons (45 type 2 diabetic patients and 20 normal control) (32 male,33 female) with mean age (46.95  $\pm$ 7.459) enrolled in this study. The study groups are collected randomly from Al Najaf center for Diabetic and endocrine in Al Sader teaching hospital during the time between January 2016 to June 2016. TCD examination was performed in Middle Euphrates Neuroscience Center for all stuied group to assess cerebral vasoreactivity in middle cerebral artery by breath holing test,hyperventilation test (HV), Transient hyperemic test (THRR). (Statistical Package of Social Sciences) SPSS version 23 was used for the statistical analysis.

**Results :** There was highly significant change of breath holding index BHI{ between control group and diabetic group} (p.value<0.05) and significant change of HV between control group and diabetic group . Also statistical significant change in THRR in relation to glycemic control(p.value< 0.05).

**Conclusion :** There was significant changes in TCD indices that assessed cerebral vasoreactivity in breath holding index, ,hyperventilation in type2 diabetic patients compared with control subjects.

**Key words :** Diabetes mellitus; Cerebral vasoreactivity; Transcranial Doppler Ultrasonography.

## **Introduction**

Diabetes mellitus (DM), commonly referred to as a metabolic diseases that result from lack of insulin in person's blood or when their body has a problem using the insulin it produces (the insulin resistance)<sup>[1]</sup>.Symptoms of high blood

sugar include frequent urination(polyuria), increased thirst(polydepsia), and increased hunger(polyphagia). If left untreated, diabetes can cause many complications.<sup>[2]</sup>

Acute complications can include diabetic ketoacidosis,nonketotic hyperosmolar coma, hypoglycemia, or death<sup>[2]</sup>.Serious long-term complications include stroke, heart disease,chronic kidney failure,foot ulcers, and damage to the eyes.<sup>[3]</sup>

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.<sup>[3]</sup>

Cerebral vasomotor reactivity is defined as a shift between cerebral blood flow or cerebral blood velocity before and after administration of a potent vasodilatory stimulus test, and also it's a unique physiologic characteristic of the brain related to the intrinsic ability of cerebral arteries to alter their caliber in response to a vasoactive stimulus<sup>[4].</sup>

Diabetes increases the risk for cerebromicrovascular disease. possibly through its effects on blood flow regulation<sup>[5]</sup>. Cerebral microvascular disease in diabetes has been attributed to the effects of chronic hyperglycemia on capillary structure, endothelial reactivity<sup>[6]</sup>, and blood-brain barrier permeability, thus affecting regional metabolism and blood flow regulation<sup>[7]</sup>.Given that more than one million people are diagnosed with diabetes yearly, a Diabetic patients compose roughly 6.3% of the U.S. population but account for 15-27% of all incident strokes. estimates<sup>[8,9]</sup>.When based on 2002 considering age-adjusted incidence rates, diabetic patients are 2.9 times as likely to have a stroke compared with nondiabetic patients, a disparity that is seen in multiple racial/geographic groups<sup>[10,11,12]</sup> This is due specifically to an increase in the rate of ischemic stroke rather than hemorrhagic stroke<sup>[13]</sup> .Most diabetes mellitus (DM) patients are either hyperglycemic and/or

exhibit insulin resistance. Both these conditions have been postulated to trigger endothelial dysfunction and atherosclerosis, which contribute to the underlying pathogenesis of stroke<sup>[14]</sup>. This might have served as rationale for previous studies that showed DM to be an of independent risk factor stroke stroke<sup>[15-17]</sup> or TIA<sup>[18,19]</sup>. general ischemic

Cerebral vasoreactivity has been generally assessed by positron emission tomography [21] (PET) ,single-photon emission computed tomography (SPECT) [20,21], and transcranial Doppler (TCD) [22] ultrasonography .These methods investigate the residual capacity of cerebral arteries to dilate in response to an increase carbon dioxide of  $(CO_{2}),$ via CO<sub>2</sub> inhalation, breath-holding test (BHT), or acetazolamide (ACZ) administration.

An alternative to either PET or SPECT in CVR the evaluation of is TCD ultrasonography, a simple and noninvasive technique that allows rapid measurements of flow velocities in large cerebral arteries. With a vasodilatory stimulus, it has also provided CVR assessment in healthy subjects and in patients with carotid artery steno-occlusive disease <sup>[23,24]</sup> Studies using TCD have also suggested that impaired CVR is predictive of cerebral ischemic patients<sup>[25]</sup> events in such .Current applications of TCD in adults and children include vasospasm in sickle cell disease <sup>[26]</sup> ,subarachnoid haemorrhage (SAH) <sup>[27]</sup>, intra- and extracranial arterial stenosis and occlusion<sup>[28,29]</sup>, brain stem death , head injury, raised intracranial pressure (ICP)' intraoperative monitoring <sup>[30]</sup>, impaired function cerebral vasomotor and microembolism in right to left cardiac shunts<sup>[31]</sup>.

# <u>Methodology</u>

#### Study design

The current study of case–control design included 65 persons (45 type 2

diabetic patients and 20 normal control) with age group (30-60 years).

#### Patients

The patient are collected randomly from Al Najaf center for Diabetic and endocrine in Al Sader teaching hospital during the time between January 2016 to June 2016.

**Inclusion criteria**:Type 2 diabetic patients, age of patients was >30 years old, and sufficient transtemporal window.

Exclusion criteria.: Hypertension, anaemia, History of asthma or chronic obstructive pulmonary disease (COPD), History of cerebrovascular disease, transient ischaemic attack (TIA), complete stroke or extracranial or intracranial steno-occlusive lesions or altered cerebral hemodynamic,Coronary disease,Autonomic neuropathy artery excluded by doing some tests for patients like heart rate response to deep breathing ,heart rate response to standing up,blood pressure response to standing up and blood pressure response to sustaind handgrip) under supervision of clinical neurologist, Medication like beta blocker and calecium

channel blocker, Smoking and alcoholic, Polycythemia and haematological disease.

#### Instrument

By using transcranial Doppler(TCD) pulse wave doppler(M.mode) with 2 MH frequency probe with transcranial software,Atys company French.

#### Method

#### History

A uniform case sheet was assigned for every participant in the study which include age ,sex, history of smoking ,medical history, family history, drug history and DM(duration and treatment).

#### Examination

Full examination specially neurological examination was done for all patients

including motor, sensory and autonomic examination were undertaken to exclude diabetic neuropathy by consultant neurologist wit experience in the field. Body weight and height were measured by digital weight and height scale.body mass index was calculated according to the following equation<sup>[32,33,34]</sup>(BMI= wight (Kg)/ height(m<sup>2</sup>).Blood pressure measurement and ECG also done for all study groups.

#### **Biochemical analysis**

Sample of blood were taken from all study group for laboratory investigation fasting blood sugar (after 12 hour overnight fasting) and HbA1C.

#### TCD examination

TCD was performed in supine position. Probe was positioned over each transtemporal window, arteries of the Willis circle were insonated by standard protocol and mean blood flow values (MBFV) were recorded.

Vasoreactivity to  $CO_2(CO_2R)$  was measured using 1.5 minutes of hyperventilation. Before proceeding to the definitive recording, all subjects were trained to perform the procedure of breath holding and hyperventilation correctly.

Determination of vasomotor reserve (VMR) with the transcranial Doppler-Co2 (TCD-CO2) by three tests:

- 1. Breath holding test for induction of cerebral vasodilitation by breath hold for 40 seconds.
- 2. Hyperventilation test by asking the patient to hyperventilate for 1.5 minuts.
- 3. Transient hyperemic test by pressure on common carotid artery and then relive the pressure ,this test for assess cerebral autoregulation.

• Findings of our study are taken to study the relationship of breath holding index, hyperventilation, transient

hyperaemic response by TCD with age ,gender, BMI, HBA1C. TCD parameters or indices and CVR were studied among type2 diabetes compare with control.

#### **3.5:Statistical analysis**

Data were expressed as mean  $\pm$  SD.

Independent-sample t-test had been used to compare the difference between diabetic and normal groups. Statistical analysis was performed by using computer programs Statistical Package of Social Sciences (SPSS) version 23 and Microsoft excel in data performing. (statistical significance was obtained at p<0.05 value).

# **Results**

Table 1: Demographic and clinico- biochemical characteristics of studied population shows that the current study included 65 subjects (45 subjects were known case of T2DM) and 20 ( as control group ).

| Variables       | Variables Control |             | Total     |  |
|-----------------|-------------------|-------------|-----------|--|
| Age (30-45 yrs) | 11 (55.0%)        | 16(35.6%)   | 27(41.5%) |  |
| (46 and more )  | 9(45.0%)          | 29(64.4%)   | 38(58.5%) |  |
| Sex F           | 10(50.0%)         | 23 (51.1%)  | 33(50.8%) |  |
| Μ               | 10(50.0%)         | 22 (48.9%)  | 32(49.2%) |  |
| BMI <25         | 4(20.0%)          | 5 (11.1 %)  | 9(13.8%)  |  |
| ≥25             | 16(80%)           | 40 (88.9%)  | 56(86.2%) |  |
| HbA1C <7        | 20(100%)          | 12(26.7 %)  | 32(49.23) |  |
| ≥7              | 0(0.0%)           | 33 (73.3 %) | 33(50.77) |  |

Table 2: Cerebral vasoreactivity of diabetic patients versus control goup shows that there was a highly significant statistical association of BHI{ between control group and diabetic group} (p.value<0.05) and significant change of HV between control group and diabetic group while no significant change in THRR between study group.

| Parameter                     | Diabetic<br>No%=45 (69%)<br>Mean ± SD | Control<br>No%=20(31%)<br>Mean ± SD | P-value |
|-------------------------------|---------------------------------------|-------------------------------------|---------|
| Breath holding index          | 0.4604±0.24493                        | 0.7360±0.23493                      | 0.000   |
| Hyperventilation              | $23.8786 \pm 12.93330$                | 28.0000±6.4563                      | 0.042   |
| Transient hyperaemic response | $1.140 \pm 0.154$                     | 1.17±0.171                          | 0.546   |

Table 3: Effect of gender on Cerebral vasoreactivity in diabetic patient shows that there was no significant statistical association in BHI,HV,THRR p.value> 0.05 in male and female diabetic patients.

| Parameter                     | Sex | No.<br>% | Mean ± SD            | P-value |
|-------------------------------|-----|----------|----------------------|---------|
| Breath holding index          | Μ   | 22(49%)  | $0.4968 \pm 0.24175$ | 0.335   |
|                               | F   | 23(51%)  | $0.4291 \pm 0.25062$ |         |
| Hyperventilation              | Μ   | 22(49%)  | 28.3750±11.48906     | 0.926   |
|                               | F   | 23(51%)  | 28.0204±13.69641     |         |
| Transient hyperaemic response | Μ   | 22(49%)  | 1.1714±0.193         | 0.225   |
|                               | F   | 23(51%)  | 1.1152±.09940        |         |

Table 4: Effect of age on cerebral vasoreactivity in diabetic patient shows that there was no significant statistical change in BHI,HV,THRR (p.value> 0.05) between age groups in diabetic patients.

| Parameter                           | Age                | No.<br>%           | Mean ± SD   | P-value |
|-------------------------------------|--------------------|--------------------|---|---------|
| Breath holding index                | (30-45)<br>(46-65) | 16(36%)<br>29(64%) | $\begin{array}{c} 0.5075 {\pm}\ 0.29659 \\ 0.4345 {\pm}\ 0.21256 \end{array}$ | 0.344   |
| Hyperventilation                    | (30-45)<br>(46-65) | 16(36%)<br>29(64%) | 32.4856±13.64855<br>25.8259±11.41558  | 0.088   |
| Transient<br>hyperaemic<br>response | (30-45)<br>(46-65) | 16(36%)<br>29(64%) | $\begin{array}{c} 1.1038 \ \pm 0.10720 \\ 1.1641 \ \pm \ 0.17226 \end{array}$ | 0.211   |

Table 5: Effect of glycemic control on cerebral vasoreactivity in diabetic patients shows evaluation of CVR in diabetic goup in relation to glycemic control. There is no significant statistical association in BHI,HV between two groups of glycemic control but show statistical significant change in THRR (p.value< 0.05).

| Parameter                        | HBA1C                                  | No.<br>%           | Mean ± SD                          | P-value |
|----------------------------------|--|--------------------|------------------------------------|---------|
| Breath holding index             | Controlled<br>DM<br>uncontrolled<br>DM | 13(29%)<br>32(71%) | 0.4162 ± .26918<br>0.4784 ± .23652 | 0.442   |
| Hyperventilation                 | Controlled<br>DM<br>uncontrolled<br>DM | 13(29%)<br>32(71%) | 29.0192±14.412<br>27.8584±11.907   | 0.782   |
| Transient<br>hyperaemic response | Controlled<br>DM<br>uncontrolled<br>DM | 13(29%)<br>32(71%) | 1.2146±.21616<br>1.1134±.11152     | 0.044   |

Table 6 : Effect of body mass index on cerebral vasoreactivity in diabetic patients shows that there was no significant stastical association in BHI, HV, THRR in two group of assessment of body mass index (BMI) but the majority of patients in group had a BMI >25.

| Parameter                        | BMI                       | No.<br>%           | Mean ± SD                                  | P-value |
|----------------------------------|---------------------------|--------------------|--|---------|
| Breath holding index             | Normal BMI<br>Over weight | 10(22%)<br>35(78%) | $0.4500 \pm .19568$<br>$0.4634 \pm .25973$ | 0.881   |
| Hyperventilation                 | Normal BMI<br>Over weight | 10(22%)<br>35(78%) | 32.777 ± 13.72742<br>13.72742 ±12.0469     | 0.193   |
| Transient hyperaemic<br>response | Normal BMI<br>Over weight | 10(22%)<br>35(78%) | $1.1100 \pm .11804$<br>$1.1520 \pm .162$   | 0.453   |

## **Discussion**

In this study, 65 subjects (45 T2DM & 20 control ) studied to evaluate cerebral vasoreactivity through middle cerebral artery by measuring breath holding index and subsequent hyperventilation and transient hyperaemic response.

# ✤ Comparison of cerebral vasoreactivity of diabetic patients versus control group

In current study, which involved 45 type 2 diabetic patients , reveals significant change of BHI,HV (p.value<0.05) which suggest impaired cerebral vasoreactivity ,compared to 20 control group. The results are in agreement with results of Paola Palazzo et al., 2013<sup>[35]</sup>, who reported that impaired cerebral vasoreactivity in type2 diabetic patients in compared with control group. This may explained by impaired VMR in this selected population of T2DM patients strongly suggests that insulinresistance has an impact on vascular function, even in the absence of metabolic derangement. Activation of oxidative stress pathways, by increased glucose variability<sup>[36]</sup>, might also have a negative impact on endothelial function.

Effect of age and gender on cerebral vasoreactivity in diabetic patient.

In our study, show no statistical significant change in BHI, HV, THRR p.value> 0.05 between age groups in diabetic patients. This may explained by effect of diabetes that overcomes the physiological effect of age and gender on cerebral vasoreactivity.

This result agree with David Last et al.,2007<sup>[37]</sup>, which adressed the regional effects of type 2 diabetes and associated conditions on cerebral tissue volumes and cerebral blood flow (CBF) regulation, the result demonstrate no differ in age, sex between diabetic and control groups. This finding agree with Yamamoto et al., 1980 [38] examined the effect of aging on vasodilator responses cerebral to hypercapnia and found that mean CBF in the elderly was  $\approx 10\%$  to 20% less than in young volunteers and that vasodilatory response to hypercapnia in elderly patients without risk factors was similar to that in young volunteers.

But the results disagree with Vladimira Vuleti *et al.*,2011<sup>[39]</sup>, to assess cerebral vasoreactivity (CVR) in type 2 diabetes mellitus (DM2)by transcranial doppler and factors which may influence on it. In DM2 group they found a significant correlation between BHI and age (p=0.0004),fasting glycemia (p=0.04), and albuminuria

(p=0.04) (creatinine clearance in multivariate analysis (p=0.007)).

#### ✤ Effect of glycemic control on cerebral vasoreactivity in diabetic patient

Analysis of effect of glycemic control on cerebral vaoreactivity in diabetic patients did not reveal any siginificant correlation by BHI,HV,but statistical significant changes in THRR.

This result agree with Vladimira Vuleti et al.,2011, to assess cerebral vasoreactivity (CVR) in type 2 diabetes mellitus (DM2)by transcrainial doppler and factors that did not find any correlation between the HbA1c and CVR in diabetic patients by BHI.

# ✤ Effect of body mass index on cerebral vasoreactivity in diabetic patient.

In current study, there was no significant change in BHI, HV, THRR in assessment of body mass index (BMI). This result disagree with Magdy Selim, et al., 2008<sup>[40]</sup>, which is cross sectional study aimed to determine the effects of high body mass index (BMI) on cerebral blood flow regulation in patients with type-2 diabetes mellitus, hypertension, and stroke that 90 controls, 30 diabetics, 45 include hypertensives, and 32 ischemic stroke patients who underwent transcranial Doppler for evaluation of blood flow velocities (BFV) in the middle cerebral arteries (MCA) and cerebrovascular resistance (CVR) during supine rest and head-up tilt. On the other hand, this findings inconsistent with Kadoi, Y., et al.,2003 <sup>[41]</sup>, that show that HbA1c is related to an impaired vasodilatory response to CO<sub>2</sub>. This discrepancy might be due in part to differences in demographic data like age, sex, duration of diabetes, exclusion criterian in addition to collection of sample like Kadoi, Y., et al.,2003 used in their study diabetic patients with retinopathy.

## **Conclusion**

There was significant association in TCD indices that assessed cerebral vasoreactivity (BHI,HV,THRR) in type2 diabetic patients compared with control subjects. These results may carry important implications for the preventive strategies in treatment of DM2 patients.

While no correlation with age ,sex,BMI.

# **Recommendations**

- 1. Large sample size to get awide range to study cerebral vasoreactivity.
- 2. TCD examination should be performed periodically as a routine basis for all diabetic patients because the TCD is the most accurate method in the evaluation and monitoring cerebral of the haemodynamic changes in the diabetic microangiopathy, especially silent ones.
- 3. Long-term prospective studies should be performed in order to evaluate the clinical course of cerebrovascular impairment and endothelial dysfunction in the natural history of diabetic disease.

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تقييم تفاعلية الاوعية الدموية الدماغية لدى مرضى السكري من النوع الثاني باستخدام جهاز دوبلر الدماغ(TCD)

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الخلاصة

خلفية الدراسة:

يرتبط النوع الثاني من داء السكري مع زيادة مخاطر الإصابة بأمراض القلب والأوعية الدموية والدماغية ومع ارتفاع معدلات الوفيات والإعاقة. تفاعلية الاوعية الدموية الدماغية واحدة من العلامات الأكثر دقة لديناميكية الدم الدماغي، وقد تبين أنها تضعف في الاشخاص مع مرض اختزال انسداد الشريان السباتي ويرتبط بزيادة مخاطر الانسدادات في الشرايين الدماغيه جهاز دوبلر الدماغ استخدم لقياس تفاعلية الاوعي الذين يعانون من زيادة مخاطر الفراعي مع معن التبط النوعية الدماغية واحدة من العلامات الأكثر دقة لديناميكية الدم الدماغي، وقد تبين أنها تضعف في الاشخاص مع مرض اختزال انسداد الشريان السباتي ويرتبط بزيادة مخاطر الانسدادات في الشرايين الدماغيه جهاز دوبلر الدماغ استخدم لقياس تفاعلية الاوعية المولية المخاطر ولوضع خطة الفراليان للعلام.

<u>الهدف:</u> الهدف من الدراسة هو تقييم تفاعلية الاوعية الدموية الدماغيه لدى مرضى داء السكري من النوع الثاني باستخدام جهاز دوبلر الدماغ.

<u>المنهجية:</u> خمسة وستين شخص (45 من مرضى السكري النوع الثاني و 20 الاشخاص السليمين ) (32ذكورا و 33 اناثا) معدل اعمار هم(7.459± 46.95 عاما) التحقو في هذه الدراسة. تم جمع مجموعات الدراسة عشوائيا من مركز النجف لمرضى السكري والغدد الصماء في مستشفى الصدر التعليمي خلال الفترة ما بين كانون الثاني 2016 إلى حزيران 2016. فحص دوبلر الدماغ أجريت لجميع فريق الدراسة في مركز الفرات الاوسط للعلوم العصبية لتقييم تفاعلية الاوعية الدموية الدماغيه في الشريان الدماغي الأوسط من خلال اختبار حبس التنفس ، اختبار فرط التنفس ، اختبار استجابة فرط الرياس العابر. تم استخدام برنامج حزمة التحليل الاحصائية للعلوم الاجتماعية النسخة 23 للتحليل الإحصائي.

<u>النتائج:</u> اظهرت النتائج ان هناك تغيير كبير في اختبار حبس التنفس {بين مجموعة مرضى السكري والاشخاص السليمين} (القيمة الاحتمالية <0.05) وتغير ملموس في اختبار فرط التنفس بين, الاشخاص السليمين ومجموعة مرضى السكري. التغيير أيضا ذات دلالة إحصائية في فيما يتعلق بمكافحة نسبة السكر في الدم (القيمة الاحتمالية <0.05) السكر في الدم (القيمة الاحتمالية حرور) الموية الدماغيه في مرضى السكري من النوع الثاني مقارنة مع الاشخاص السليمين. المفاتيح: داء السكري. تفاعلية الاوعية الدماغية دوبلر الدماغ.