



# Pulpal blood flow in streptozotocin-induced diabetic rats measured by laser Doppler flowmetry

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## Abstract

**Objective** The aim of this study is to investigate the pulpal blood flow in streptozotocin-induced diabetic rats by using laser Doppler flowmeter

**Materials and methods** The animal model of streptozotocin (STZ)-induced diabetic rats (i.v. injection of STZ 55 mg/kg BW) was used. Thirty-two male Sprague-Dawley rats weighing 200-250 g were divided equally into 2 groups; non-diabetes (CON) and diabetes (STZ). At 12 weeks (wks) and 24 wks after the STZ injection, the laser Doppler flowmeter (Model ALF 21, USA.) was used to measure pulpal blood flow of the right lower incisor while the animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg BW).

**Results** The present study demonstrated that STZ-rats developed hyperglycemia (blood glucose,mg/dl: CON-rats =  $85.13 \pm 8.69$ , STZ-rats =  $402.88 \pm 24.81$  at 12 wks; CON-rats =  $98.00 \pm 5.11$ , STZ-rats =  $327.75 \pm 16.08$  at 24 wks), higher glycosylated hemoglobin levels (glycosylated hemoglobin,%: CON-rats =  $3.68 \pm 0.05$ , STZ-rats =  $10.86 \pm 0.24$  at 12 wks; CON-rats =  $3.41 \pm 0.09$ , STZ-rats =  $11.20 \pm 0.38$  at 24 wks), higher mean arterial blood pressure (mean arterial blood pressure,mmHg: CON-rats =  $93.75 \pm 6.48$ , STZ-rats =  $114.50 \pm 2.80$  at 12 wks; CON-rats =  $87.29 \pm 2.44$ , STZ-rats =  $115.00 \pm 8.09$  at 24 wks), and loss of body weight (body weight,g: CON-rats =  $424.88 \pm 5.08$ , STZ-rats =  $183.38 \pm 8.87$  at 12 wks; CON-rats =  $487.88 \pm 13.52$ , STZ-rats =  $333.38 \pm 28.15$  at 24 wks) Plasma level of vitamin C in STZ-rats was significantly lower than CON-rats (plasma vitamin C,g/l: CON-rats =  $1.30 \pm 0.15$ , STZ-rats =  $0.62 \pm 0.02$  at 12 wks; CON-rats =  $1.24 \pm 0.10$ , STZ-rats =  $0.65 \pm 0.08$  at 24 wks). The decrease of pulpal blood flow in intact right lower incisor was observed in STZ-rats (pulpal blood flow,ml/min/100g tissue: CON-rats =  $30.40 \pm 1.95$ , STZ-rats =  $16.73 \pm 2.77$  at 12 wks; CON-rats =  $29.54 \pm 3.08$ , STZ-rats =  $16.09 \pm 1.58$  at 24 wks).

**Conclusion** By using laser Doppler flowmeter, the present study shows the decrease of pulpal blood flow in streptozotocin-induced diabetic rats.

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**Key words:** laser Doppler flowmetry; pulpal blood flow; rats; streptozotocin-induced diabetes

## Introduction

Diabetes mellitus (DM) is a common metabolic disorder with several major complications affecting the quality of life. There are two major forms of DM. Type 1 DM is associated with a defect or an absence of the insulin-producing beta cells of the pancreas.<sup>1</sup> In this type, originally known as insulin-dependent DM, the patient needs exogenous insulin for survival. Type 2 DM, which occurs because of an impaired function of the beta cells or resistance to insulin effects, was previously referred to as non-insulin-dependent DM.<sup>1</sup> Diabetes mellitus is associated with an increased risk of hypertension, atherosclerosis and disorder of microcirculation. There is increasing evidence to suggest that vascular endothelial dysfunction may play a major role in these complications.<sup>2</sup> Endothelial dysfunction has been suggested to be an early event in diabetic vascular disease.<sup>3</sup> The development of endothelial dysfunction is characterized by an impairment in vasorelaxation and increased adhesiveness of the endothelial cell lining. There is currently great interest in the potential contribution of increased oxidative stress to the development of complications in DM. Increase production of oxygen-derived free radicals and decrease antioxidant defense mechanism have been described in DM.<sup>4</sup> Vitamin C (ascorbic acid) is one of the most powerful natural antioxidant in human. With its antioxidant property, vitamin C can scavenge oxygen-derived free radicals and spares other endogenous antioxidants from consumption.<sup>5,6</sup> It has been reported that plasma and tissue levels of vitamin C are lower in diabetic compared to nondiabetic subjects.<sup>7</sup> There are many suggestions regarding origins of oxidative stress in DM including free radical reactions related to glycation of proteins, consumption of nicotinic-adenine dinucleotide phosphate through the polyol pathway, glucose autoxidation, hyperglycemia-induced pseudohypoxia, and activation of protein kinase C.<sup>7,8</sup>

Oral health has been reported to be an important impacts on systemic health.<sup>9</sup> There are various oral manifestations of DM, such as xerostomia and an increased incidence of dental caries and periodontitis. Severity and prevalence of periodontitis are increase in DM, especially in uncontrolled diabetic patients. Recently, it has been suggested that periodontitis is added as one of the complications of DM.<sup>10</sup>

Dental pulp, surrounded by low-compliance layers of dentine, has a physiological environment very different from that of other tissues. Pulpal tissues from the

diabetic patients were characterized by the presence of large vessel and small vessel angiopathies and a thickened basement membrane. Many of the samples from diabetic patients contained numerous sickle-shaped calcifications that occluded vessels. These data suggest that diabetic patients experience both vascular changes and calcifications in the dental pulp.<sup>11</sup>

In spite of the intensive research for DM and oral health, no report has been shown the characteristic of dental pulp blood flow in DM. This may be due in part to technical difficulties resulting from the small size of pulp tissue enclosed in rigid walls of dentine and enamel. Since the oxygen-derived, free radical-generating system has been found to affect blood flow within the pulp,<sup>12</sup> the production of oxygen-derived free radicals in diabetes may also have a role in the alteration of pulpal vascular tone. In addition, laser Doppler flowmetry method is generally accepted for pulpal blood flow measurement.<sup>13,14</sup> Therefore, the present study was designed to determine the pulpal blood flow in streptozotocin-induced diabetic rats by using laser Doppler flowmetry.

## Materials and Methods

Thirty-two male Sprague-Dawley rats weighing 200-250 g were used in this study. Rats were divided equally into 2 groups : non-diabetes and diabetes. To induce DM, streptozotocin (STZ) (Sigma Chemical Co.) was freshly prepared by dissolving in citrate buffer pH 4.5 (Sigma Chemical Co.) and immediately injected into the tail vein of fasted rats, at a dose of 55 mg/kg BW. Hyperglycemia (glucose concentration > 200 mg/dl) was confirmed by measurement of glucose concentration in blood samples obtained from the tail vein 48 hours after the STZ- injection. Blood glucose was determined by using glucometer (Advance Glucometer, Boehringer Mannheim, Germany). Rats treated with STZ that did not exhibit an elevation of blood glucose level at 48 hours were excluded from the study. The control rats were injected with citrate buffer (pH 4.5). The experiments were performed in eight animals of each group at 12 and 24 weeks after the injection of STZ or citrate buffer, the time period that the diabetic vascular complication of this animal model has been shown to fully developed.<sup>15</sup>

On the day of experiment, body weight was measured and rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg BW). Laser Doppler flowmeter (Advance Company, Model ALF 21, USA.) was used to measured pulpal blood flow. With this model, the absolute flow value is calculated and displays. The flowmeter was calibrated according to the manufacturer's instructions. The probe was fixed with a micro-manipulator at right angles to the distal surface of the rat

right lower incisor.<sup>16</sup> After pulpal blood flow measurement, tracheostomy was performed. A catheter was inserted into a carotid artery for measuring arterial blood pressure and collecting blood. Arterial blood pressure was measured by using Polygraph system (NIHON KOHDEN, Japan) and was reported in term of mean arterial blood pressure. Blood glucose, glycosylated hemoglobin (HbA<sub>1c</sub>), and plasma vitamin C level were determined after the end of the experiment. Blood glucose was determined by using glucometer. Glycosylated hemoglobin was analyzed from whole blood using colourimetric method. Plasma vitamin C level was measured using enzyme-assisted spectrophotometric method.

**Data analysis**

Results were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed with Student's *t* test, with a significant acceptance level of *p* < 0.05.

**Results**

The injection of STZ 55 mg/kg BW into Sprague-Dawley rats resulted in polyglycemia within 48 hours and showed persistent hyperglycemia throughout the experiment. In the present study, the criteria used for diabetic rats was the blood glucose that higher than 200 mg/dl. The results shown in Table 1 indicated that STZ-induced diabetic rats (STZ-rats) exhibited hyperglycemia, higher HbA<sub>1c</sub> levels, and loss of body weight compared to the non-diabetic control rats (CON-rats) at both period measured. The plasma level of vitamin C in STZ-rats were significantly lower than CON-rats (Fig.1). Mean arterial blood pressure of STZ-rats were significantly higher than those of controls. Pulpal blood flow in the intact right lower incisor of STZ-rats were significantly lower than the CON-rats (Fig.2).

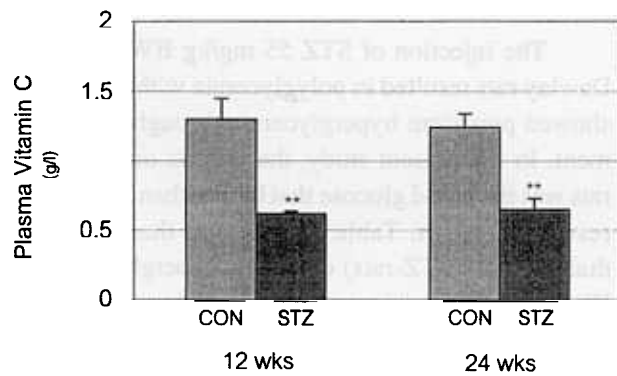
**Table 1** Means ± SEM of body weight, blood glucose, glycosylated hemoglobin, mean arterial blood pressure, plasma vitamin C, and pulpal blood flow of control rats (CON) and streptozotocin-induced diabetic rats (STZ).

	12 weeks		24 weeks	
	CON	STZ	CON	STZ
Body weight (g)	424.88 ± 5.08	183.38 ± 8.87***	487.88 ± 13.52	333.38 ± 28.15*
Blood glucose (mg/dl)	85.13 ± 8.69	402.88 ± 24.81***	98.00 ± 5.11	327.75 ± 16.08***
Glycosylated hemoglobin (%)	3.68 ± 0.05	10.86 ± 0.24***	3.41 ± 0.09	11.20 ± 0.38***
Mean arterial blood pressure (mmHg)	93.75 ± 6.48	114.50 ± 2.80*	87.29 ± 2.44	115.00 ± 8.09**
Plasma vitamin C (g/l)	1.30 ± 0.15	0.62 ± 0.02**	1.24 ± 0.10	0.65 ± 0.08**
Pulpal blood flow (ml/min 100g tissue)	30.40 ± 1.95	16.73 ± 2.77*	29.54 ± 3.08	16.09 ± 1.58**

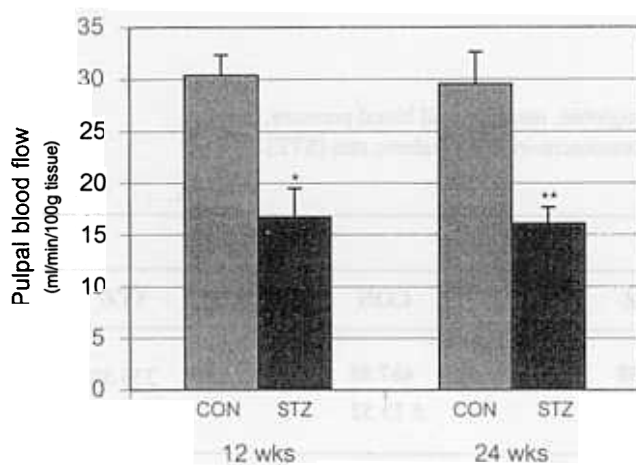
\* significantly difference as compared to CON at the same period (*p* < 0.05).

\*\* significantly difference as compared to CON at the same period (*p* < 0.01).

\*\*\* significantly difference as compared to CON at the same period (*p* < 0.001).



**Fig.1** Plasma vitamin C of control rats (CON) and streptozotocin-induced diabetic rats (STZ) at 12 weeks and 24 weeks after streptozotocin injection. \*\*  $P < 0.01$  vs age-matched control rats.



**Fig. 2** Pulpal blood flow of control rats (CON) and streptozotocin-induced diabetic rats (STZ) at 12 weeks and 24 weeks after streptozotocin injection. \*  $P < 0.05$ , \*\*  $P < 0.01$ , vs age-matched control rats.

## Discussion

Streptozotocin, pancreatic  $\beta$ -cell cytotoxin, is the most useful agent for the induction of experimental DM.<sup>17,18</sup> The general metabolism of STZ-induced diabetic rats is similar to that in human DM.<sup>19</sup> Thus for these reasons, we used STZ to induce diabetes. In the present study STZ-induced diabetic rats developed hyperglycemia and higher mean arterial blood pressure. Body weight in control group was significantly greater than that in experimental group. Our results are in agreement with those obtained by Nishikata<sup>20</sup> and Sasaki<sup>21</sup> and suggest that STZ-induced damage to the pancreas has a broad influence on the general metabolism of the rat.

Laser Doppler flowmetry, a non-invasive electro-optical technique which allows the semi-quantitative recording of pulpal blood flow, was used in this study. This technique has facilitated the analysis of pulpal blood flow under various experimental conditions in animal and human teeth.<sup>16,22,23</sup> Its advantages are that it can be performed in intact teeth and gives absolute values for pulpal blood flow. The development of a non-invasive method for assessment of blood circulation within the dental pulp, and thus direct measurement of pulpal vitality, would be a major advance in clinical practice.

It is known that an adequate blood supply to the dental pulp is essential to the health of the tooth. The blood flow in the dental pulp, a highly vascularized tissue,<sup>24,25</sup> is regulated by a variety of endogenous mediators. Pulpal blood flow is influenced by neurogenic factors as well as by several substances such as norepinephrine, 5-hydroxytryptamine, isoproterenol, and bradykinin.<sup>26-28</sup> Pulpal blood flow is also affected by chemico-physical factors such as temperature and experimental tooth movement<sup>29,30</sup> as well as in response to inflammation.<sup>31,32</sup> Oxygen free radicals has also been reported to affect pulpal blood flow.<sup>12</sup>

In this study, STZ-induced diabetes was found to decrease the pulpal blood flow. It is now accepted that the production of oxygen-derived free radicals in diabetes may contribute to alterations in local blood flow.<sup>33-36</sup> The principal effect of oxygen free radicals is vasodilation, but they can also evoke vasoconstriction. The free radical has been reported to produce vasoconstriction in the dental pulp.<sup>12</sup> This could be explained by the destruction of basally released endothelium-derived relaxing factor and/or endothelial dysfunction. Mechanisms of endothelial dysfunction in diabetes individuals are not clear, but there is a strong evidence that inactivation of nitric oxide, the endothelium-derived relaxing factor, by increased oxygen-derived free radicals could be responsible.<sup>37</sup> The study of Lohinai et al. suggested that, similar to the other tissues, a nitric-oxide-dependent basal vasodilator tone exists in the dental pulp.<sup>38</sup> Numerous studies of DM and long-term diabetic complications support the conclusion that there is an association between DM and oxidative stress.<sup>33-36</sup> A number of pathologic studies have shown that endogenous antioxidants are not sufficient to protect against excessive oxidative stress.<sup>39-41</sup> Up to now, hyperglycemia is very well documented as a cause of higher plasma free radical production,<sup>42</sup> and the decrease in antioxidative defense mechanisms.<sup>43</sup> The examination of the antioxidant status in hyperglycemic state by Cerialleo et al. showed that the increased oxygen free radical production associated with a reduction in plasma antioxidants,

particularly vitamin C.<sup>44</sup> In the present study, after STZ injection, hyperglycemia was developed. Moreover, plasma vitamin C reduction was also demonstrated in both monitored time points of STZ-diabetic rats. These results implied that the oxidative stress generation during DM may lead to disturbances of pulpal blood flow. However, the exact mechanism can not be drawn out since the pulpal tissue level of vitamin C, antioxidative enzyme, and free radical formation are not measured in this experiment. Therefore, in order to investigate the relationship between oxidative stress and pulpal blood flow in DM, more research should be provided.

### Conclusion

By using laser Doppler flowmeter, our study shows the decrease of blood flow in the diabetic dental pulp. Since the potential contribution of increased oxidative stress to the development of vascular complication in diabetes has been reported. The reduction in antioxidant defense mechanism observed in this study may responsible for the diabetic-induced decrease in pulpal blood flow. However, further investigations and analyses are needed.

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# ปริมาณการไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟันของ หนูแรทที่ถูกเหนี่ยวนำให้เป็นเบาหวานด้วยสเตรปโตโซโตซิน เมื่อวัดโดยเลเซอร์ดอปเปลอร์โฟลเมทรี

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## บทคัดย่อ

**วัตถุประสงค์** เพื่อศึกษาปริมาณการไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟันของหนูแรทที่ถูกเหนี่ยวนำให้เป็นเบาหวานด้วยสเตรปโตโซโตซิน โดยวัดด้วยเครื่องเลเซอร์ดอปเปลอร์โฟลมิเตอร์

**วัสดุและวิธีการ** ศึกษาในหนูแรทพันธุ์ Sprague-Dawley เพศผู้ น้ำหนัก 200-250 กรัม แบ่งหนูออกเป็น 2 กลุ่มคือ กลุ่มหนูควบคุมและกลุ่มหนูเบาหวาน หนูถูกเหนี่ยวนำให้เป็นเบาหวานโดยการฉีดสเตรปโตโซโตซินขนาด 55 มิลลิกรัม ต่อน้ำหนักตัว 1 กิโลกรัมเข้าทางหลอดเลือดดำที่หาง ทำการวัดปริมาณการไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟันของฟันหน้าล่างขวาของหนูทั้ง 2 กลุ่มด้วยเครื่องเลเซอร์ดอปเปลอร์โฟลมิเตอร์ ในสัปดาห์ที่ 12 และสัปดาห์ที่ 24 หลังจากฉีดสเตรปโตโซโตซิน โดยวัดในขณะที่ทำให้หนูสลบด้วยการฉีดโซเดียมเพนโทบาร์บิทอลขนาด 50 มิลลิกรัม ต่อน้ำหนักตัว 1 กิโลกรัมเข้าทางช่องท้อง

**ผลการศึกษา** หนูที่ถูกเหนี่ยวนำให้เป็นเบาหวานมีระดับน้ำตาลในเลือดและระดับฮีโมโกลบินที่มีน้ำตาลเกาะสูงขึ้น (น้ำตาลในเลือด, มิลลิกรัม/เดซิลิตร: หนูควบคุม=85.13±8.69, หนูเบาหวาน=402.88±24.81 ที่ 12 สัปดาห์; หนูควบคุม=98.00±5.11, หนูเบาหวาน=327.75±16.08 ที่ 24 สัปดาห์; ฮีโมโกลบินที่มีน้ำตาลเกาะ, %: หนูควบคุม=3.68±0.05, หนูเบาหวาน=10.86±0.24 ที่ 12 สัปดาห์; หนูควบคุม=3.41±0.09, หนูเบาหวาน=11.20±0.38 ที่ 24 สัปดาห์) ความดันเลือดแดงเฉลี่ยสูงขึ้น (ความดันเลือดแดงเฉลี่ย, มิลลิเมตรปรอท: หนูควบคุม=93.75±6.48, หนูเบาหวาน=114.50±2.80 ที่ 12 สัปดาห์; หนูควบคุม=87.29±2.44, หนูเบาหวาน=115.00±8.09 ที่ 24 สัปดาห์) น้ำหนักตัวลดลง (น้ำหนักตัว, กรัม: หนูควบคุม=424.88±5.08, หนูเบาหวาน=183.38 ± 8.87 ที่ 12 สัปดาห์; หนูควบคุม=487.88±13.52, หนูเบาหวาน=333.38±28.15 ที่ 24 สัปดาห์) ระดับวิตามินซีในพลาสมา มีค่าลดลง (วิตามินซี, กรัม/ลิตร: หนูควบคุม=1.30±0.15, หนูเบาหวาน=0.62±0.02 ที่ 12 สัปดาห์; หนูควบคุม=1.24±0.10, หนูเบาหวาน=0.65±0.08 ที่ 24 สัปดาห์) ปริมาณการไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟันมีค่าลดลง (ปริมาณการไหลของเลือด, มิลลิตร/นาท./เนื้อเยื่อ 100 กรัม: หนูควบคุม=30.40±1.95, หนูเบาหวาน=16.73±2.77 ที่ 12 สัปดาห์; หนูควบคุม=29.54±3.08, หนูเบาหวาน=16.09±1.58 ที่ 24 สัปดาห์)

**สรุป** ปริมาณการไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟันของหนูแรทที่ถูกเหนี่ยวนำให้เป็นเบาหวานด้วยสเตรปโตโซโตซินเมื่อวัดโดยใช้เครื่องเลเซอร์ดอปเปลอร์โฟลมิเตอร์พบว่ามีค่าลดลง

(ว ทันต จุฬฯ 2546;26:221-7)

**คำสำคัญ:** การไหลของเลือดที่เลี้ยงเนื้อเยื่อในโพรงฟัน เบาหวานที่ถูกเหนี่ยวนำด้วยสเตรปโตโซโตซิน เลเซอร์ดอปเปลอร์โฟลเมทรี หนูแรท