Chapter 11
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The Recovering Arterial Blood Flow Access to the Rhomboid Fossa Causes Restoring the HbA1c Level in Pre-Diabetic Patients

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ABSTRACT

The present study demonstrates the recovery of cervical vertebral arterial blood flow access to the rhomboid fossa causes the restoration of HbA1c levels for patients with pre-diabetic (pre-DM) conditions. HbA1c is formed due to the chemical condensation of hemoglobin and glucose, which are present in high concentrations in red blood cells. The first research results established a relationship between HbA1c and vascular complications. The measurement method used is HPLC. When measured in an NGSP-certified laboratory, a change in HbA1c of at least 0.5% is considered statistically and clinically significant. The observation is in good agreement with the consideration of the human body as a dissipative structure. Such consideration is the focus of the recently announced theory of centralized aerobic-anaerobic energy balance compensation (TCAAEBC). According to it, observed connections between high blood pressure (HBP) and the lifted level of HbA1c can be linked to the obstruction of arterial blood flow access to rhomboid fossa (OABFARF), causing the delivery of incorrect information on blood oxygen availability. Below we provide detailed information on how in this case TCAAEBC explains the very initiation of multiple chronic non-communicable diseases (NCDs), starting with type 2 diabetes mellitus (DM). Diabetes mellitus is a metabolic disorder reflecting

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the complex integration of body systems, care must be taken in selecting the correct animal model for use in various in vivo experiments. Mouse models are used in experimental studies of obesity and type 2 diabetes to identify the role of inflammation, insulin resistance, and other potential treatments, and the knowledge gained from such studies has been accurately applied to humans with this diagnosis.

Keywords: Diabetes mellitus; TCAAEBC; blood pressure; arterial hypertension; obstruction of arterial blood flow access to rhomboid fossa.

1. INTRODUCTION

The largest issue of civilization is persistent non-communicable diseases (NCDs), according to the current concepts of the World Health Organization. Cardiovascular diseases and diabetes are the main types of NCDs [1]. Cardiovascular diseases (17.9 million patients) and diabetes (2.0 million) also contribute to the structure of mortality from NCDs. The leading risk factors for death from NCDs worldwide are high blood pressure (BP), which accounts for 19% of all deaths worldwide, and high blood glucose (prediabetes and diabetes) [2]. The main methods of treatment for the above disorders are drug therapy, while non-drug methods for the treatment of arterial hypertension (AH) and normalization of glucose levels are mentioned as additional in current recommendations [3-5].

2. GLYCATED HEMOGLOBIN HBA1C

HbA1c is formed due to the chemical condensation of hemoglobin and glucose, which are present in high concentrations in red blood cells. This process occurs slowly and continuously over the lifespan of red blood cells, which averages 120 days. In addition, the rate of HbA1c formation is directly proportional to the average glucose concentration in the erythrocyte during its life cycle [6]. Therefore, as chronic hyperglycemia increases, so does HbA1c production. This makes it an excellent indicator of overall glycemic control over the 120-day lifespan of normal red blood cells. The last 30 days before the test have the greatest influence—50% of the HbA1c value is due to them [7]. For example, if a patient has recently experienced an acute change in glycemic control (e.g., glucocorticoid treatment), the HbA1c value will be disproportionately affected by the most recently measured glucose level [8,9].

There are two approaches to measuring HbA1c. One approach separates HbA1c from other hemoglobin fractions and involves methods such as chromatography and electrophoresis. Another approach aims to identify HbA1c as an antigen using methods such as immunochemistry [10]. In this context, the four most commonly used methods for determining HbA1c are ion-exchange high-performance liquid chromatography (HPLC), boronate affinity HPLC, immunoassay, and enzymatic assay [11]. Unfortunately, the variety of assays used to measure HbA1c has resulted in a lack of standardization, limiting the ability to reliably determine the value. This lack of standardization led the

International Expert Committee (IEC) to oppose the use of HbA1c for the diagnosis of diabetes mellitus in 1997 [12]. To address this problem, the Glycohemoglobin Standardization Program (NGSP) was created in 1996 to standardize HbA1c measurements. The first research results established a relationship between HbA1c and vascular complications. The measurement method used is HPLC. When measured in an NGSP-certified laboratory, a change in HbA1c of at least 0.5% is considered statistically and clinically significant [13,14].

Over the past few years, new sampling and analysis capabilities have emerged. Although the use of rapid tests has been shown to improve HbA1c measurements [15], there is a lack of evidence from randomized clinical trials [16]. In addition, different analysis methods are available that have varying accuracy compared to the NGSP certification criteria [17]. Interestingly, there appear to be significant racial and ethnic differences in HbA1c values for a given mean glucose value. For example, Caucasians have been reported to have approximately 0.1% to 0.4% lower absolute HbA1c for the same average glucose level compared with other ethnic groups such as Hispanics, blacks, or Asians. The reasons for these differences remain unclear [18]. Any condition that prolongs the life of a red blood cell or is associated with a decrease in red blood cell turnover exposes the cell to glucose for a longer period, resulting in higher HbA1c levels. Iron deficiency anemia is a common disease associated with falsely elevated HbA1c levels. Studies conducted in patients with and without diabetes have shown that treatment of iron deficiency anemia reduces HbA1c levels by 16–18%, although the exact mechanism remains unclear [19]. Other conditions associated with decreased red blood cell turnover are also associated with falsely elevated HbA1c levels, including vitamin B-12 and folic acid deficiency anemia [20,21].

Likewise, any condition that shortens the lifespan of a red blood cell or is associated with increased red cell turnover reduces the cell's exposure to glucose, resulting in a decrease in HbA1c levels. Conditions such as acute and chronic blood loss, hemolytic anemia, and splenomegaly can lead to falsely low HbA1c results [19]. Patients with end-stage renal disease tend to have falsely low HbA1c values. This is primarily due to chronic anemia, accompanied by decreased erythrocyte survival [22]. HbA1c levels may not accurately reflect glycemic levels during pregnancy, mainly due to a decrease in red blood cell lifespan from 120 to 90 days, as well as an increase in erythropoietin production [23]. HbA1c values decrease during pregnancy by 12–16 weeks pregnancy with a further decrease, which stabilizes by the 20th week of pregnancy [24-26]. HbA1c levels may begin to rise again in the third trimester [27]. Because HbA1c values tend to be falsely low during pregnancy, HbA1c should not be used to diagnose gestational diabetes. Instead, an oral glucose tolerance test should be used for screening and diagnosis, and glucose control during pregnancy should be determined primarily through self-monitoring of blood glucose. HbA1c values between 4% and 5.9% are considered normal. In diabetes, HbA1c levels increase, which indicates a greater risk of developing retinopathy, nephropathy, and other complications. The International Diabetes Federation recommends

keeping your HbA1c level below 6.5%. An HbA1c value greater than 8% indicates that diabetes is not well controlled and therapy should be changed.

3. ARTERIAL HYPERTENSION AND DIABETES

Common symptoms of diabetes are extreme thirst, frequent urination, increased fatigue, weight loss, and decreased vision. According to the National Institutes of Health website, 73.6% of patients with diabetes mellitus aged 18 years or older also have AH [28]. AH is traditionally considered a consequence of diabetes [29, 30]. However, data from the ARIC study (Atherosclerosis Risk in Communities), the CARDIA study (Coronary Artery Disease Risk in Young Adults), and the Framingham Heart Study offspring, which included 10,893 people, showed that hypertension is a risk factor for the development of diabetes and often precedes its development [31]. Further, it will be shown that, based on the theory we propose, AH is an important symptom of diabetes.

The connection between arterial hypertension, diabetes and brain behavior: Despite more than a century of research in this area, there is still no generally accepted theory explaining the underlying etiology of essential hypertension. Research has primarily focused on the kidney and peripheral vasculature to better understand this condition. The search for a new point of view on the nature of AH became possible after the discovery of the Cushing reflex. In 1902, Harvey Cushing observed a proportional increase in blood pressure after brainstem ischemia caused by increased intracranial pressure (ICP) in conscious dogs [32]. He hypothesized that this response exists to protect the brain from decreased blood supply in the acute situation of increased intracranial pressure. The exact pathogenesis of the Cushing's reflex remains unclear [33]. The possibility that ICP is not the sole cause of the Cushing reflex itself arises from the fact that the response to blood pressure occurs before the increase in intracranial pressure [33]. Experiments conducted by Schmidt and colleagues showed that the Cushing reflex is controlled by the autonomic nervous system since its physiological changes are related to the balance of the sympathetic nervous system and parasympathetic nervous system [34]. However, the specific relationship between the autonomic nervous system response and the Cushing reflex and its symptoms was not explained before the development of the TCAAEBC [35]. Dickinson and Thomson suggested that the Cushing mechanism might represent more than simply an attempt to maintain blood flow in the brainstem [36]. They conducted a large postmortem study of 80 patients and found that antemortem blood pressure values were correlated with the narrowing of the cervical vertebral arteries. With other vessels examined, including the carotid, femoral, and renal arteries, and this correlation was not as strong. They suggested that narrowing of the cervical vertebral arteries with subsequent brainstem hypoperfusion may be a cause of AH rather than a consequence, but they had no evidence to support a causal relationship [37].

Further, the focus in research increasingly shifted toward clarifying the role of the brain in increasing blood pressure. One of the reasons for this shift in emphasis is the growing evidence of hyperactivity of the sympathetic nervous system in

people with essential hypertension [38-42]. The mechanisms responsible for this remain unclear. Experimental data on rats with AH and observations in humans suggest that blood flow to the brain may be important for establishing the operating level of excitation of the sympathetic nervous system (SNS) and blood pressure [37,42].

With the emergence of the Selfish Brain Theory (SBT), the brain began to be given a special place in research into the causes of AH. SBT was proposed in 2004. This theory examines energy exchange in the body. Before SBT, it was postulated that the energy needs of the brain, muscles, and organs were met in parallel. The brain is considered by SBT as the system that controls the body, which consumes a quarter of the body's energy and considers the satisfaction of its needs to be paramount. Therefore, he is always looking for ways to obtain energy to maintain homeostasis [43]. Initially, SBT focused on explaining the mechanisms of obesity. Further, the boundaries of applicability of the theory began to expand: studies appeared that clarified the Cushing mechanism and its connection with AH. AH was often observed in overweight people. It has been suggested that a decrease in medulla oblongata perfusion causes a reflex reaction of the SNS, and an increase in peripheral vascular resistance and hypertension [44]. A relationship has been shown between blood pressure and brainstem perfusion, arterial constriction in the cervical spine, and the brainstem in various animal models (giraffes, rats) [44-46]. The connection is interpreted as follows: the brain stem responds to any decrease in blood flow to the control centers of the cardiovascular system by activating pathways (in particular, the SNS) aimed at counteracting the changes and maintaining a homeostatic level of perfusion. Brainstem hypoperfusion is a key component of Cushing's mechanism. Sympathetic constriction of the peripheral arteries occurs in response to insufficient cerebral perfusion. Interestingly, this mechanism is physiological in growing giraffes, where gravitational hypotension of the brain causes vasoconstriction and an increase in blood pressure to allow blood flow to the brain [44]. It has also been suggested that the metabolic mechanism changes from oxidative to non-oxidative during the narrowing of the arteries in the brain stem to obtain the energy needed by the brain [44].

Evidence from animal models of hypertension suggests that high blood pressure may develop as a vital mechanism for maintaining adequate blood flow to the brain. It has been demonstrated that vertebrobasilar artery hypertrophy in rats occurred before the onset of AH [44]. The authors also showed that brainstem ischemia caused by bilateral clamping of the cervical vertebral artery resulted in a large increase in SNS activity in hypertensive rats compared with age-matched normotensive animals [42]. In addition, the brainstem of rats with AH is susceptible to hypoxia, and this is aggravated by the normalization of blood pressure [47]. Also, within the framework of SBT, when studying the mechanisms of brain hypoperfusion, it was suggested that hypertension is a protective function of the brain [48]. However, despite obvious progress in the study of the relationship between the brain and AH, the causes and detailed mechanism of the occurrence of high blood pressure within the framework of SBT remain unclear [49].

Within the framework of this theory, the occurrence of diabetes is considered a result of the stress response of the brain. Stress, according to SBT, is a high level of uncertainty. The brain is hypothesized to have two ways of reducing uncertainty or expected free energy. First, the brain can use arousal from stress to immediately reduce uncertainty and adapt, to learning. Habituation has been shown to minimize free energy by expanding preferences, behaviors, and how to respond to stress. It has been shown how addiction reduces the average energy consumption of the brain, which in the long term can lead to the development of type 2 diabetes with obesity. For some people experiencing stress, addiction does not occur because, for them, addiction itself, the use of free energy is not the optimal solution, in such cases toxic stress occurs. Toxic stress increases the average energy consumption of the brain, which in the long term can lead to the development of type 2 diabetes. Increased energy consumption by the brain, overloading the cardiovascular system, can also lead to the development of myocardial infarction and stroke.

The emergence of TCAAEBC in the early 2000s marked a new stage in the study of the relationships between the cervical arteries, AH, and the brain. When treating cervical osteochondrosis using manual techniques, patients experienced concomitant normalization of blood pressure [50] (Fig. 1). These observations served as the starting point for research into the root causes of high blood pressure in the body. It was suggested that AH is a reaction of the brain to receive information from the oxygen availability detector located in the rhomboid fossa of the cerebellum. With cervical osteochondrosis, the arteries are pinched: the speed of blood flow decreases, and the access of oxygen to the detector decreases. It is assumed that the brain interprets this as a lack of available oxygen. Next, to protect itself from hypoxia and to maintain energy balance, the brain sends a signal to the heart to increase heart rate and blood pressure. Several studies have shown a connection between blood flow disturbances in the cervical vertebral arteries and arterial hypertension [51-52]. TCAAEBC incorporated TEM and explained the relationship between cervical arterial blood flow, AH, and the brain.

Theory of centralized aerobic-anaerobic energy balance compensation: TCAAEBC considers a living organism as a quasi-stable dissipative structure with a feedback system: such a structure is always far from equilibrium, and at the same time it continues to exchange matter, information, and energy with the environment to maintain homeostasis [53]. Life events can lead to deformation in the cervical region of the spinal column, which is a conductor of information about the state of the body to the place where this information is analyzed. Here, the vertebral arteries pass through the transverse processes of the vertebrae, their lumen naturally narrows the blood flow to the brain and any displacement in this area can lead to compression of the vessels. As a result, blood flow decreases, the vessels narrow, and less oxygen-rich arterial blood flows to the detectors in the cerebellum. Based on the information received, the brain interprets that there is less oxygen in the external environment, although there is enough of it. Next, the brain will do work to return the oxygen level to its previous level. At first, he tries to do this in an energetically advantageous way at the

expense of external resources—an aerobic compensation mechanism. Aerobic compensation responses are neurogenic cardiovascular responses that result in a sustained increase in blood pressure, resting peripheral capillary constriction, and an increase in heart rate. As is known, the aerobic mode of respiration is energetically more favorable: with aerobic glycolysis, the energy output is 38 ATP molecules, and with anaerobic glycolysis, it is only 2 ATP molecules [54].

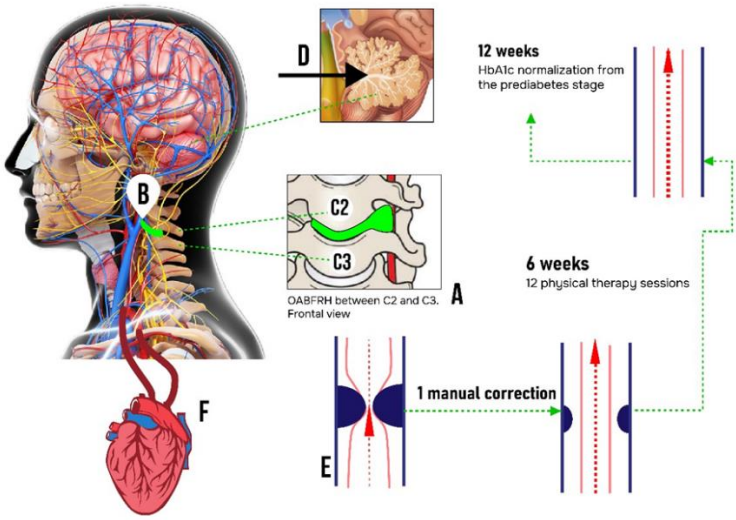

Fig. 1. A – localization of intervertebral disc disorders between the C2 and C3 vertebrae, causing OABFARF. B-positioning of events A on the neck B - cerebellum D - rhomboid fossa F - heart E-schematic demonstration of OABFARF, elimination of OABFARF after manual correction and further facilitation of blood flow in the cervical arteries

If this situation is repeated many times, then the brain, to avoid premature wear and tear of the heart muscle, rearranges biochemical processes under conditions of reduced oxygen flow. The less energetically advantageous anaerobic compensation mechanism is activated. Anaerobic compensation reactions are neurohumoral metabolic reactions that lead to an increase in the anaerobic metabolism of sugars, phospholipids, and other energy-intensive biochemical compounds [55]. Anaerobic compensation reactions, being less energy efficient, are launched only when the energy reserves of aerobic compensation reactions are completely depleted. Next, the aerobic-anaerobic balance shifts towards anaerobic, thus maintaining the overall energy balance. According to TCAAEBC, the total energy of the body, an open dissipative system, E_{CONST} is the sum of the energy components during aerobic and anaerobic compensation. The body will always strive to do work against the “external” equilibrium (according to Bauer’s universal law of biology [56]) to keep the value of this energy constant and to maintain homeostasis:

$$E_{CONST} = E_{AE} + E_{AN},$$

where E_{AE} is the energy level for aerobic compensation, and E_{AN} is for anaerobic compensation.

According to this expression, prolonged use of anaerobic compensation mode by the brain can lead to further complications in the body, for example, to the state of prediabetes [57,58]. When maintaining homeostasis in the body in this way, glycolysis will release by-products (lactates, etc.), the accumulation of which contributes to the emergence of new diseases.

Therapy of Arterial Hypertension and Diabetes based on the theory of centralized aerobic-anaerobic energy balance compensation: To restore access to blood flow to the oxygen sensor located in the rhomboid fossa, it is necessary to open the lumen to normalize the linear velocity of arterial blood flow through the cervical vertebral arteries. The therapy consists of two parts — a one-time manual correction and subsequent strengthening:

1. Correction of cervical intervertebral discs is performed manually to restore blood flow in the cervical vertebral arteries. It all starts with determining the location of the zone of hypertonicity in the collar zone and neck muscles. Hypertonicity is relieved by pressing on the muscles in the sagittal plane. It is performed by pressing with the thumb on the occipitovertebral muscles located between the transverse processes of C1–C7. Pressure is applied in the same way to the muscles of the cervical spine. During these manipulations, the patient is in a lying position. A detailed description of the sequential steps has recently been published [20–52, 59]. The above procedure allowed to restoration of blood flow in the cervical vertebral arteries.
2. After correction, strengthening exercises are performed, which make it possible to create a muscle corset to correct the geometry of the lumen after recovery [51]. The correction is usually followed by a cycle of 12 visits devoted to corrective exercises. Their goal is to strengthen the muscular corset of the neck. These visits lasted from 14 to 40 days [55].

Thus, the normalization of blood flow through the vertebral arteries as a result of the use of the author's manual correction technique can have a significant therapeutic effect in individuals with AH and prediabetes.

4. REVIEW OF ANIMAL MODELS

The first models of AH appeared during the study of the mechanisms of the Cushing reflex in dogs [37]. A relationship between intracranial pressure and AH was observed. Further studies of the Cushing mechanism demonstrated the relationship between AH and brain perfusion using mouse, rat, and giraffe models [42,44,46,47,48]. Studies [60-63] have shown that stimulation of the rabbit anterior cervical ganglion, but not distension of the vertebral artery, can cause an increase in blood pressure. There is also evidence that activation of the

goat's superior cervical ganglia (SCG) leads to increased blood pressure [64]. The arterial blood supply in rats demonstrates a heterosegmental organization [65]. Removal of the implant returned blood pressure to normal values.

Although several in vitro and silico studies have been conducted and improved over the past decades, animal models remain the most effective for understanding the complex etiology and multisystem interactions present in diabetes mellitus [66]. Many diabetes studies are conducted on rodents, while some studies are also conducted on larger animals. Experimental animals used in the study of diabetes mellitus can be divided into three types, such as animals with genetic diabetes mellitus, various models, and other models based on methods of inducing experimental diabetes mellitus [67]. Diabetes can develop in experimental animals either spontaneously or with the help of chemical drugs [67a].

Animal models can be created through two main mechanisms: disease induction (e.g. use of specific drugs) or genetic manipulation. Both are important because they allow the analysis of specific disease-related mechanisms and are important for understanding the pathogenesis and progression of the disease and extrapolating to humans. Since diabetes mellitus is a metabolic disorder reflecting the complex integration of body systems, care must be taken in selecting the correct animal model for use in various in vivo experiments [68]. To achieve this goal, the selection of a diabetic animal model requires careful consideration of the specific aspects of the disease and the specific knowledge targeted by each study [69]. Animal models are classified depending on the type of diabetes they simulate, as well as the mode of induction, such as spontaneous or induced [70,71]. In addition, transgenic and donor mouse models exist, but their use in research remains questionable [72,67a].

Mouse models are used in experimental studies of obesity and type 2 diabetes to identify the role of inflammation, insulin resistance, and other potential treatments, and the knowledge gained from such studies has been accurately applied to humans with this diagnosis [73,67a].

5. CONCLUSION

Despite the tremendous success of the approach based on TCAAEBC in treating human patients from different NCDs, there are some issues that could be resolved, based solely on the working animal model. Between such issues are, e.g.

1. The dynamics of the manifestation’s development (onset)
2. The relationship between the severity of NCDs and the extent of OABFARF
3. Differences in the consequences of OABFARF on right and left side

All above mentioned questions as well as some others need to be answered before TCAAEBC can be recommended for the practical needs of the wide medical community.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (Chat GPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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