MEDICINE & HEALTH

2021



Editors
Assoc. Prof. Dr. Hakan KAYA
Assist. Prof. Dr. Hüseyin KAFADAR

MEDICINE & HEALTH 2021
Editors
Assoc. Prof. Dr. Hakan KAYA
Assist. Prof. Dr. Hüseyin KAFADAR

EFE ACADEMY PUBLISHING

MEDICINE & HEALTH 2021

Editor
Assoc. Prof. Dr. Hakan KAYA
Hüseyin KAFADAR

EFEACADEMY

Medicine & Health 2021

Editor: Hakan KAYA
ORCID (0000-0002-5925-5150)

Editor: Hüseyin KAFADAR
ORCID (0000-0002-6844-7517)

ISBN: 978-625-7601-75-7
First Edition: May 2021

Bu eserin; yayın, satış ve kopyalama hakları EFE AKADEMİ'ye aittir.

LIBRARY CARD

MEDICINE & HEALTH 2021
KAYA, Hakan – KAFADAR, Hüseyin
First Edition, 326 p., 160 x 240 mm.

Design: İsa Burak GÜNGÖR (burakgungor@efeakademi.com)
Cover Design: Duygu DÜNDAR (dundar.duygu@gmail.com)

Certificate No: 43370

Printing House Certificate No: 43370

Efe Akademi Yayınevi
Yıldız Teknik Üniversitesi Davutpaşa Kampüsiçi Esenler / İSTANBUL
0212 482 22 00
www.efeakademi.com

Matbaa Adres:
Ofis2005 Fotokopi ve Büro Makineleri San. Tic. Ltd. Şti.
Yıldız Teknik Üniversitesi Davutpaşa Kampüsiçi Esenler / İSTANBUL
0212 483 13 13
www.ofis2005.com

THE DEFINITION OF DIABETES INSPIDUS BY THE WORD "DIABETES" IS A MISNOMER: REASONS AND RISKS REQUIRING A NAME CHANGE

Zafer SAHIN

- Affiliation: Karadeniz Technical University, Faculty of Medicine, Department of Physiology, Trabzon, Turkey
- ORCID: 0000-0001-7982-7155
- Mail: zafersahin55@yahoo.com, zafersahin@ktu.edu.tr

Introduction

Diabetes mellitus and diabetes insipidus share the first word of their name due to their similarity of several symptoms (polyuria and polydipsia). However, in fact, the cause and treatment of these two diseases are quite different. Diabetes mellitus, simply diabetes, occurs when the pancreas does not produce enough insulin (or insulin resistance) to control the amount of glucose (sugar) in the blood, while Diabetes insipidus occurs when the kidney's inability to concentrate urine due to lack of inadequate antidiuretic hormone (ADH, also known as arginine vasopressin (AVP)) and unresponsiveness to ADH. In other words, Diabetes mellitus is a pancreatic disorder, whereas Diabetes insipidus is a hypothalamo-pituitary-kidney disorder. Therefore, these nomenclatures are an example of the misnomer in medicine that these two diseases are referred to by similar names, and we think it is time to change the name diabetes insipidus. In this manuscript, it is aimed to evaluate the negative (or dangerous) aspects of this situation which should not be seen as an ordinary name similarity and draw attention to this topic. For this reason, it is planned to clarify the topic in light of the following questions: Why are the same first names used for these two distinct diseases? Is it correct to call two different diseases with similar names because of the similarity of only a few symptoms? Is name similarity a convenience for medical approaches or is it quite dangerous? In conclusion, the best way to avoid all these negativities or problems is a name change. The basic principle in name change should be to emphasize the impaired physiological functions rather than symptoms. Therefore, 'neurogenic insipidus' may be used for central diabetes insipidus and 'nephrogenic insipidus or renal insipidus' may be used for nephrogenic diabetes insipidus. A nomenclature may also be made by highlighting the hormone name. In this case, central ADH deficient and renal ADH deficient may be alternative names.

Why Are The Same First Names Used For These Two Distinct Diseases?

Diabetes mellitus and diabetes insipidus are referred to under the common nomenclature diabetes. Therefore, it is useful to explain the meaning of the term diabetes. As far as we know, the name Diabetes was first used by Demetrius of Apameia, a physiologist, in the 1st-2nd century BC (Areteus the Cappadocian, 1856). Moreover, the first written document

on polyuria dates back to 1500 years BC in the Egyptian Papyrus Ebers that is an ancient written text of medical knowledge (Guthrie & Humphreys, 1988; Reece, 1995). The term "diabetes" was based on Ionic and Latin terms, meaning 'to pass or run through' as in a siphon. It is considered that the first clinical comment of diabetes mellitus was given by Areteus of Cappadocia (AD 30-90) as 'because the fluid does not remain in the body but uses the man's body as a ladder whereby to leave it' (Areteus the Cappadocian, 1856). Although these data illustrate the first recognition of diabetes, some medical historians suggest that the first attempt at defining the signs of diabetes was made by Aulus Cornelius Celsus (30 BC-50 AD). It is said that Celsus mentioned a disease with frequent and excessive urination as well as marked emaciations without pain (Medvei, 1993; Southgate, 1999; Zajac et al., 2010). As another important piece of knowledge, it is stated that Apollonius Memphites, an Egyptian scientist (in approximately 230 BC), used the "diabetes" prefix for the first time to indicate excessive urine passage and attributed its etiology to the kidney (Papaspyros, 1964). The first test for diabetes was the urine taste test. Early Egyptians, Asians and Indians pointed out the sweet taste of urine. In about 500 BC, two Indian doctors (Chakrat and Sushrut) observed that ants congregated around someone's urine because of the taste of the urine (Tattersall, 2010). Likewise, Chang Chung-Ching (AD 229) indicated that 'the urine was so sweet that dogs liked it' (Guthrie & Humphreys, 1988). It is known that some animals and insects flock to sweet urine spills (Guthrie & Humphreys, 1988; MacCracken & Hoel, 1997). Both Avicenna (AD 980-1037) and Paracelsus (AD 1493-1541) later suggested tasting the urine of diabetics (Guthrie & Humphreys, 1988; Kenyan & Nagy, 2005). However, the Greek physician Claudius Galen (AD 129-200) considered diabetics' urine was unchanged in terms of drinking (Guthrie & Humphreys, 1988). We understand that sweetness in and/or large amounts of urination have been associated with diabetes in the historical process. As a result, the name diabetes was accepted as a nomenclature, regardless of the location and cause of disorders.

In 1674, Thomas Willis reintroduced the presence of a sweet material in the urine of diabetic patients in his book 'Pharmaceuticalice Rationalis', although the actual substance was still unknown (Tattersall, 2010; Willis, 1684; McGrew, 1985). His work raised new attention in diabetes research. In 1682, an important development related to diabetes mellitus occurred. A 29-year-old young scientist, Johann Brunner (1653-1727), performed an

experimentally partial pancreatectomy on a dog and then observed excessive thirst, polydipsia and polyuria symptoms in the dog. Although Brunner did not make a specific definition, this study was an important first step that would benefit future researchers on the role of the pancreas in the pathogenesis of diabetes mellitus (Willis, 1684; Farmer, 1952; Mann, 1971).

Towards the end of the 1800s, biochemical methods were developed to determine the presence of glycosuria. Based on patients with and without sugar in their urine, to differentiate these two different forms of the disease, Johann Frank (1745-1821) categorized diabetes as diabetes vera (sweet urine) and diabetes insipidus (tasteless urine). The basis of this classification was Avicenna's first observations of people with excessive urination (Frank, 1794). Between the 18th and 19th centuries, it began to be revealed that the previously known type of diabetes is type 1 diabetes, while the presence of type 2 diabetes was also revealed (McGrew, 1985).

Definitions related to diabetes insipidus date back to 225 years ago. In 1794, Johann Peter Frank of the University of Pavia introduced the term diabetes insipidus, which is characterized by prolonged and sugar-free excessive urination that is not related to kidney disease (Frank, 1794). The term inspiration is derived from the French word 'insipide', which means ' tasteless'.

In the following period, a hypothalamus-related disorder was found to be responsible for diabetes insipidus. In 1901, Magnus and Shaffer showed that the posterior pituitary extract had a vasoconstrictor and antidiuretic activity (Magnus & Shaffer, 1901). In the following years, posterior pituitary extracts were successfully used to treat diabetes insipidus (Farini, 1913; Von den Velden, 1913). In relation to the pathophysiology of the disease, Bailey & Bremer, and Ranson have experimentally determined that diabetes insipidus occurs in animals with supraoptico-hypophyseal tract injury that connects the hypothalamic supraoptic nucleus with the posterior pituitary (Bailey & Bremer, 1921; Ranson, 1937). Again, in an experimental study, Camus and Roussy discovered in dogs that puncturing the hypothalamus but keeping the pituitary gland intact, produces polyuria (Camus & Roussy, 1920). When we reached the 1920s, the available evidence was conclusive enough to describe diabetes insipidus as a disorder of the pituitary gland, and the disease was thought to be a hypopituitary syndrome (Marañón, 1921; Motzfeldt, 1918). Today, synthetic ADH analogues, not posterior pituitary extracts, are used in the treatment of central diabetes insipidus.

Regarding nephrogenic diabetes insipidus, De Lange first identified DI patients who did not respond to posterior pituitary extracts. He also found that this disease was seen among family members, but the disease was not transferred from male to male (De Lange, 1935). These observations have led to a more accurate analysis by Forssman, who provided important information on nephrogenic diabetes insipidus. Forssman found that the kidney has a critical role in this form of diabetes insipidus resistant to treatment with posterior pituitary extracts. He assumed that this was caused by a special defect in tubular reabsorption of water and appeared more common in boys (Forssman, 1945; Waring & Tappan, 1945). Today, this definition still remains valid as the congenital nephrogenic Diabetes Insipidus form linked to the X chromosome (Valenti & Tamma, 2016). In fact, the nomenclature of nephrogenic diabetes insipidus was formalized by Williams and Henry in 1947 for the syndrome characterized by polyuria and renal concentrating impairment, but unaffected by ADH treatment. They also noticed that the disease was inherited from the asymptomatic female to male offspring (Williams & Henry, 1947).

It is understood that the word diabetes has been mentioned in cases related to polyuria from the past to the present. This included assessments of the taste or content of urine over time. In this process, sugar-containing polyuria cases were defined as diabetes mellitus, and in other cases, polyuria cases were classified as diabetes insipidus.

Apart from the historical documentation of diabetes mellitus, perhaps, this expression may be the first piece of data on the lesser-known historical story of diabetes insipidus. In other words, it is not possible to say that there is diabetes mellitus in everyone who has excreted more urine in the old periods just like today. Therefore, Claudius Galen may have witnessed diabetes insipidus in ancient times.

Is It Correct To Call Two Different Diseases With Similar Names Because Of The Similarity Of Only A Few Symptoms?

Concerning the two main forms of diabetes nowadays, in the 1670s, Thomas Willis pointed out that the urine taste of polyuric subjects was different compared to healthy individuals (Cannon, 1955; Eknoyan, 2010; Eknoyan & Nagy, 2005). He used the definition of diabetes as a general term in relation to polyuric individuals with sweet urine. After about a century,

his characterization resulted in the naming of people with polyuric but not sweet urine as diabetes insipidus (Valenti & Tamma, 2016).

Diabetes mellitus is a disorder of the pancreas and insulin hormone lack (Type 1 diabetes mellitus) or resistance (Type 2 diabetes mellitus), while diabetes insipidus is a disorder associated with the hypothalamus-pituitary-kidney axis and ADH hormone deficiency (neurophysin-related or other unknown causes (central diabetes insipidus)) or ineffectiveness (receptor-related (nephrogenic diabetes insipidus)). In the section above, the historical process, which provides reasons for the fact that the first names of these two diseases are the same, is mentioned. In the light of all these historical data, it is understood that polyuria, which is a common symptom in both diseases, is the cause of the common name due to its interpretation in the process extending to the present. However, the cause and character of polyuria in diabetes mellitus is quite different from diabetes insipidus. It is also known that polyuria, and as a result, thirst and polydipsia are common symptoms in these two diseases. Although the common characteristic of thirst and excessive urination is water loss in both diseases, the reason is quite different in both diseases. Unfortunately, this naming dating back to the old times has been found to be wrong over time, but it is still used as valid today.

Water loss from the extracellular fluid mainly results in hypernatremia and dehydration. An important example of this is the inadequacy/ineffectiveness of ADH secretion, which is necessary for the kidneys to retain water. In diabetes insipidus, the kidneys produce a large amount of dilute urine, and dehydration occurs, resulting in increased sodium chloride concentration in the extracellular fluid (Hall, 2016).

Glucose is reabsorbed from the proximal tubule after filtration. The amount of filtered glucose increases due to the high level of blood glucose concentration in diabetes mellitus. In healthy subjects, all glucose is reabsorbed from the proximal tubules, whereas in hyperglycemic individuals, glucose is excreted in the urine when the maximum carrying capacity of glucose from the proximal tubule is exceeded (glycosuria). This condition usually appears when the blood glucose concentration exceeds 250 mg/dL. Therefore, as a result of the osmotic diuretic effect of glucose, the volume of excreted urine increases, and polyuria occurs (Hall, 2016).

The amount of fluid excreted from the kidneys increases, and polyuria develops in both diabetes insipidus and diabetes mellitus due to two different reasons. High extracellular fluid osmolarity due to polyuria leads to excessive fluid intake (polydipsia) by activating the thirst mechanism. The fact that these few common symptoms occur in two different diseases, one related to the pancreas and disturbance of the energy metabolism, the other related to the hypothalamo-pituitary-kidney axis and the body fluid imbalance, is not a valid reason for these two distinct diseases to be referred to by the same first name. As a matter of fact, in both diseases, findings other than these common symptoms are quite different. This naturally applies to treatment. In both type 1 diabetes and type 2 diabetes, there is a dysregulation in the uptake of glucose into the cells for use for energy due to the lack or ineffectiveness of insulin. Therefore, in order to compensate for the energy deficit, the use of fats for energy with fat mobilization in diabetes mellitus has priority. As a result of intensive fat mobilization, ketone bodies such as acetoacetic and β-hydroxybutyric acid, which are formed more than the oxidation capacity of tissues, accumulate in the plasma. This condition causes metabolic acidosis in relation to the excessive increase of ketone bodies. Long-term use of fat in the liver increases the level of cholesterol in the blood and leads to the accumulation of cholesterol in the artery walls. This dysregulation is involved in the pathophysiology of arteriosclerosis and other vascular pathologies. Failure to use glucose for energy affects the use and metabolism of proteins as well as fats, and it consequently leads to the development of complications such as delay in wound healing, retinopathy, nephropathy and diabetic neuropathy in the body. Especially at the stage of hypoglycemia, in both types of diabetes mellitus, excessive eating (polyphagia) is seen in patients due to energy dysregulation. Although type 1 diabetes patients generally have a low body weight, type 2 diabetes patients often have excess weight and fat. Additionally, although the primary treatment of type 1 diabetes patients is insulin, the primary option in type 2 diabetes is weight loss or exercise, and in patients who fail to do so, thiazolidinediones (also called glitazones), metformin, sulfonylureas and insulin (in more severe cases) are also used.

The above-mentioned practices have no validity in the treatment of diabetes insipidus. In the treatment of central diabetes insipidus, ADH synthetic analogs are used to achieve water reabsorption by activating the aquaporin 2 (AQP2) channel via V2 receptors of ADH in the distal tubule and collecting tubules of the kidney. Nephrogenic Diabetes Insipidus cannot

be treated with ADH analogues due to non-responsiveness to ADH in the kidneys. Therefore, the goal of treating nephrogenic diabetes insipidus is to correct, if possible, the underlying cause of the disorder in the kidney. A low-sodium diet facilitates treatment. Additionally, hypernatremia may be improved by using some diuretics (e.g. thiazides and similar diuretics) that have an effect on increasing the excretion of sodium from the kidneys (Hall, 2016).

Is Name Similarity A Convenience For Medical Approaches Or Is It Quite Dangerous?

The major problem for individuals with diabetes insipidus is that the disease starts with the word ‘diabetes’. The prevalence and awareness of diabetes mellitus, type 1 and type 2, are incomparably greater than that of diabetes insipidus. The only concept evoked by the word ‘diabetes’ is ‘diabetes mellitus’ not only in hospital routines but also in public health-related TV programs, news, information articles and public awareness. While providing preliminary information for endocrine therapy in telephone or face-to-face appointments, this problem emerges initially. After saying the word 'Diabetes' by the patient, the term 'mellitus' will naturally come to the staff's mind before the word 'insipidus' takes place. As another important issue, the attention of the intervention team is very important, especially in patients who are unconscious or unable to speak. Undesirable results may occur due to inattention or omission. It is possible to reproduce such troubles with other examples. The worst of these negativities are situations that can result in death. A critical article about a real tragic case to draw attention to this issue was written by Malcolm Prentice, an Endocrinologist, in 2018 (Prentice, 2018). The article was published with the title ‘Time for change: Renaming Diabetes Insipidus to improve patient safety? (We recommend reading for details of the assessment). Prentice's article draws attention to the negativities associated with the pre-name 'diabetes' and is also important in terms of recommending solutions. In this part of our article, we will emphasize our name recommendation in terms of a solution to this problem. The main principle of our name proposition is that the word 'diabetes' is never used. Prentice proposed ‘Pituitary insipidus’ for central diabetes insipidus and ‘renal insipidus’ for nephrogenic diabetes insipidus. Although both name suggestions may have important proposal and acceptance, Pituitary insipidus may be confused for other pituitary insufficiencies. In

particular, there is a risk for diseases and syndromes such as hypopituitarism and hypothalamic-pituitary dysfunction (hypogonadotropic hypogonadism), which are associated with anterior pituitary hormone deficiency. For this reason, ‘neurogenic insipidus’ may be used for central diabetes insipidus and ‘nephrogenic insipidus or renal insipidus’ may be used for nephrogenic diabetes insipidus. A nomenclature may also be made by highlighting the hormone name. In this case, central ADH deficient and renal ADH deficient may be alternative names.

REFERENCES

Areteus the Cappadocian. (1856). The Extant Works. Translated & Edited: Adams F. London, England: Sydenham Society.

Bailey P, Bremer F. (1921). Experimental diabetes insipidus. *Archives of internal medicine*, 28, 773-803.

Camus JR, Roussy G. (1920). Experimental researches on the pituitary body. *Endocrinology*, 4, 507-22.

Cannon JF. (1955). Diabetes insipidus; clinical and experimental studies with consideration of genetic relationships. *A.M.A. archives of internal medicine*, 96(2), 215-72.

De Lange C. (1935). Ueber erblichen diabetes insipidus *Jahrbuch fuer Kinderheilkunde*, 145, 135.

Eknoyan G. (2010). A history of diabetes insipidus: paving the road to internal water balance. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, 56(6), 1175-83.

Eknoyan G, Nagy J. (2005). A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Advances in chronic kidney disease*, 12(2), 223-9.

Farini F. (1913). About diabetes insipidus and hypophysiotherapy. *Wien Klin Wochenschr*, 26, 1867.

Farmer L. (1952). Notes on the history of Diabetes Mellitus. *Bull NY Acad Med*, 28, 408-416.

Forssman HH. (1945). On hereditary diabetes insipidus. *Acta Medica Scandinavica*, 121.

Frank JP (1794). De curandis hominum morbis epitome. Liber 5, 38-67. Mannheim.

Guthrie DW, Humphreys SS. (1988). Diabetes urine testing: an historical perspective. *Diabetes Educ*, 14(6), 521-526.

John E. Hall. (2016). Guyton and Hall Textbook of Medical Physiology, Thirteenth edition. Elsevier Ltd Philadelphia, USA, 730-999.

Kenyan G, Nagy J. (2005). A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Adv Chronic Kidney Dis*, 12(2), 223-229.

MacCracken J, Hoel D. (1997). From ants to analogues. Puzzles and promises in diabetes management. *Postgrad Med*, 101(4), 138-5, 149.

Magnus R, Shaffer E.A. (1901) Effects of post-pituitary extracts. *Journal of Physiology*, 12, 32-8.

Mann RJ. (1971). Historical vignette "honey urine" to pancreatic diabetes: 600 B.C.-1922. *Mayo Clin Proc*, 46(1), 56-8.

Marañón (1921). Diabetes insipidus as a hypopituitary syndrome. *Endocrinology*, 5, 159-73.

McGrew RE. (1985). Encyclopedia of Medical history (1st ed., pp. 74-297). London, United Kingdom: McGraw-Hall Book Company.

Medvei VC. (1993). The Greco-Roman period. In V.C. Medvei (Ed.), The History of clinical endocrinology: a comprehensive account of endocrinology from earliest times to the present day (pp. 34-37). New York, USA: Parthenon Publishing.

Motzfeldt K. (1918). Diabetes insipidus. *Endocrinology*, 2, 111-21.

Papaspyros NS. (1964). The history of diabetes. In G. T. Verlag (Ed.), The history of diabetes mellitus. (pp. 4-5). Stuttgart, Germany: Thieme.

Prentice M. (2018). Time for change: Renaming Diabetes Insipidus to improve patient safety. *Clin Endocrinol (Oxf)*, 88(5), 625-626.

Ranson SW. (1937). Some Functions of the Hypothalamus: Harvey Lecture, December 17, 1936. *Bulletin of the New York Academy of Medicine*, 13(5), 241-71.

Reece E. (1995). The history of diabetes mellitus. In: Reece E, Coustan D, editors. Diabetes Mellitus in Pregnancy. New York: Churchill Livingstone.

Southgate TM. (1999). De Medicina. *JAMA*, 10, 921.

Tattersall RB. (2010). The history of Diabetes Mellitus. In R. Holt, C. Cockram, A. Flyvbjerg & R. Goldstein (Ed.), Textbook of Diabetes (4th ed.). Blackwell Publishing.

Valenti G, Tamma G. (2016). History of Diabetes Insipidus. *G Ital Nefrol*, 33 (Suppl 66), 33.S66.1.

Von den Velden R. (1913). The renal effects of hypophyseal extract in humans. *Berl Klin Wochenschr*, 50, 2083-2086.

Waring AJK, L. Tappan, V. (1945). A congenital defect of water metabolism. *American Journal of Diseases of Children*, 69, 323-4.

Williams RH, Henry C. (1947). Nephrogenic diabetes insipidus; transmitted by females and appearing during infancy in males. *Annals of internal medicine*, 27(1):84-95.

Willis T. (1684). Pharmaceutice rationalis, or, An exercitation of the operations of medicines in humane bodies: shewing the signs, causes, and cures of most distempers incident thereunto: in two parts: as also a treatise of the scurvy, and the several sorts thereof, with their symptoms, causes, and cure. Printed for T. Dring, C. Harper, and J. Leigh in Fleetstreet : London

Zajac J, Shrestha A, Patel P, Poretsky L (2010). The main events in the history of diabetes mellitus. In L. Poretsky (Ed.), Principles of diabetes mellitus. Springer Publishing.