Cardiovascular Diabetes Education
Your value driven partner in care

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

66: 2021 QUARTER 2: 2021

Academy

Different adipokine profiles in healthy vs unhealthy obesity

According to a research letter published in the *European Journal of Internal Medicine*, a study conducted in obese people with two distinct phenotypes revealed that those with metabolically healthy obesity (MHO) had a higher level of cardioprotective adipokines compared to those with metabolically unhealthy obesity (MUO).

The analysis included 200 obese people who had their blood sampled to measure adipokine levels, namely omentin-1, adiponectin, visfatin, resistin, and chemerin. The study calculated and compared plasma levels of adipokines in people with the MHO and MUO phenotypes.

The results show that compared to people with MUO, omentin-1 and adiponectin were increased in MHO counterparts, and visfatin, resistin, and chemerin were decreased. Significant differences were observed only for omentin-1, visfatin, and chemerin. There were no significant differences regarding demographic characteristics and cardiovascular risk factors between the two groups.

The authors conclude that the emerging higher omentin-1 and lower visfatin and resistin plasma levels in people with MHO compared to MUO counterparts could partially explain the lower cardiovascular risk of people with obesity, but without the metabolic syndrome.

These findings underline the potential prognostic role of adipose tissue in classifying people with healthy obesity at decreased cardiovascular risk.

Sanidas E, et al. Healthy and non healthy obese patients. The truth lies in the adipose tissue. ***European Journal of Internal Medicine*** **2020:4602**. https://doi.org/10.1016/j.ejim.2020.08.017

Finerenone Scores Second Pivotal-Trial Success in Diabetic Kidney Disease

Finerenone, an investigational agent from a new drug class, scored a second trial win after showing significant benefit for slowing progression of diabetic kidney disease (DKD) in people with type 2 diabetes in the FIDELIO-DKD pivotal trial (N = >5700).

In a statement released on 10 May, Bayer reported that FIGARO-DKD, a placebo-controlled trial including about 7400 people with type 2 diabetes, showed significant benefit for the primary endpoints of CV death and nonfatal CV disease. Based on the results, finerenone is currently under review by the US FDA for treatment of people with type 2 diabetes and CKD.

In addition to the primary endpoint that focused on slowing progression of DKD, FIDELIO-DKD had a secondary endpoint that assessed the combined incidence on treatment of CV death, or nonfatal stroke, MI, or hospitalisation for heart failure. Results from the study published in 2020 in the *New England Journal of Medicine* showed that finerenone was safe and effective for both endpoints. In the current FIGARO-DKD study, run at more than 1000 sites in 47 countries, these endpoints flipped. The primary outcome was a composite of CV death or nonfatal CV disease events, and the secondary outcome was prevention of DKD progression. Other than stating that the results significantly fulfilled FIGARO-DKD's primary endpoint of reducing the incidence of combined CV disease endpoints, the release gave no further outcome details.

The release noted that the cohort enrolled in FIGARO-DKD included more people with earlier-stage CKD than FIDELIO-DKD. Finerenone is a first-in-class investigational nonsteroidal, selective mineralocorticoid receptor antagonist (MRA). As an MRA, it shares certain activities with the steroidal MRAs spironolactone and eplerenone. But the absence of a steroidal structure means that finerenone does not cause steroidal adverse effects such as gynaecomastia. Results in FIDELIO-DKD showed that finerenone caused more hyperkalaemia than placebo, but the level of hyperkalaemia caused relative to spironolactone or eplerenone remains uncertain.

Finerenone Scores Second Pivotal-Trial Success in Diabetic Kidney Disease. ***Medscape*** **- May 12, 2021.**

⇒	*Advanced Glycation end-products and Vascular Complications of Diabetes*	2
⇒	*Dapagliflozin benefits T2DM consistent across kidney function groups*	3
⇒	*Pancreatic Beta Cells interact with Vagal Sensory Neurons*	4

Advanced glycation end-products and vascular complications

The role of chronic hyperglycaemia in the development of diabetes-related micro- and macrovascular complications and in neuropathy has been clearly established by intervention studies.[1-3] Various biochemical and cellular links between chronic hyperglycaemia and the microvascular and cardiovascular lesions have been proposed.[4] Among them, the advanced glycation end products (AGEs) and their specific receptors (RAGE) have been recognized as playing a pivotal role in the functional and anatomical alterations of the vessel wall.[5]

AGEs are formed during the Maillard reaction by the binding of glucose to proteins, leading to molecular rearrangements. Binding of AGEs to RAGE have been shown to activate cells, particularly monocytes and endothelial cells, resulting in the production of inflammatory cytokines, and in the expression of adhesion molecules and tissue factor.[5] AGEs also play a role in diabetes in the increase in oxidative stress and in the functional alterations in the control of vascular tone.[5] In animal models of diabetes, the administration of aminoguanidine, a potent inhibitor of AGE formation, or of recombinant RAGE which hinders AGE-RAGE, hyperpermeability and vascular lesions are prevented.[6,7] In people with T2D compared with control subjects, serum levels of AGEs and carboxymethyl lysine were found to be increased, being higher in people with retinal and/or renal complications.[8]

Some evidence has suggested that the circulating levels of the soluble isoform of RAGE (sRAGE) are associated with cardiovascular complications and death in people with T1D.[9,10]

Recently, results from the ADVANCE trial confirmed these data in people with T2D.[11] After adjusting for confounders and other risk factors, the potential association of AGE and sRAGE levels with death, major cardiovascular events, and new or worsening nephropathy was assessed, as well as the ability of sRAGE and AGE levels to reclassify the risk of nephropathy.

Serum AGE levels were independently associated with new or worsening nephropathy (Hazard Ratio 1.21 for a 1-SD increase, *P*=0.001). Serum sRAGE levels were associated with all-cause mortality (HR 1.11 for a 1-SD increase in log sRAGE, *P*=0.045). Serum sRAGE levels were also associated with new or worsening nephropathy (HR 1.20 for a 1-SD increase in log sRAGE, *P*=0.032). The accuracy of the prediction of the 5-year risk of new or worsening nephropathy was significantly improved when sRAGE and AGE results were introduced into the calculation.

"These results indicate the importance in T2D of the AGE/RAGE axis in the development of severe renal complications and in the risk of premature death."

These results indicate the importance in T2D of the AGE/RAGE axis in the development of severe renal complications and in the risk of premature death. They also emphasize the pivotal importance of correcting glucose control, namely its surrogate HbA1c, to normal values, as soon as possible in the course of the disease. Glucose control is the major and most appropriate way to prevent glycation of vascular tissues and circulating proteins, thereby preventing the development of complications.

Prof P-J. Guillausseau

References:

The DCCT Research Group. *N Engl J Med.* 1993;329:977-986.

UK Prospective Diabetes Study (UKPDS) Group. 1998;352:837-853.

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

Guillausseau PJ. *Diabetes Metab.* 1994;20:219-228.

Wautier JL, Guillausseau PJ. *Diabetes Metab.* 2001;27:535-542.

Singh R, Barden A, Mori T, et al. 2001;44:129-146.

Calcutt NA, Cooper ME, Kern TS, et al. *Nat Rev Drug Discov*. 2009;8:417–429.

Wautier MP, Massin P, Guillausseau PJ, et al. *Diabetes Metab.* 2003;29:44-52.

Thomas MC, Söderlund J, Lehto M, et al. *Diabetologia.* 2011; 54 : 2669-77.

Nin JW, Jorsal A, Ferreira I, et al. 2010;59:2027-2032.

Thomas MC, Woodward M, Neal B, et al. *Diabetes Care.* 2015;38:1891-1897

Dapagliflozin Benefits in Type-2 Diabetes Consistent Across Kidney Function Groups

The sodium-glucose co-transporter 2 inhibitor (SGLT2i) dapagliflozin has consistent cardiovascular (CV) benefits across baseline kidney-function and albuminuria levels in high-risk patients with type-2 diabetes mellitus (T2DM), according to a secondary analysis of the DECLARE-TIMI 58 trial.

"Dapagliflozin consistently reduced the relative risk of CV events irrespective of baseline estimated glomerular filtration rate (eGFR) and albuminuria status in a broad population of patients with T2DM," Dr. Thomas A. Zelniker of the Medical University of Vienna, in Austria, told Reuters Health by email.

"However," he added, "patients with both reduced eGFR and albuminuria derived significantly greater absolute risk reduction for the composite of CV death and hospitalizations for heart failure, reflecting a consistent effect in the context of their higher baseline risk."

In *JAMA Cardiology*, Zelniker et al note that SGLT2is promote urinary glucose excretion and reduce the risk for CV death and hospitalisations for heart failure in people with T2DM. However, "The extent of increased glucosuria and, therefore, the glucose-lowering efficacy of SGLT2i is attenuated in patients with worse kidney function."

To examine what impact this might have, they conducted a prespecified analysis of the DECLARE-TIMI 58 trial, a CV-outcome trial that studied the effect of dapagliflozin vs placebo in more than 17,000 participants who had or were at risk for atherosclerotic cardiovascular disease.

Participants were categorized according to baseline eGFR of below 60 mL/min/1.73 m^2 vs greater, urinary-albumin-to-creatinine ratio (UACR) of below 30 mg/g vs greater, and the number of chronic kidney disease (CKD) markers (0, 1, or 2).

The clinical efficacy of dapagliflozin was generally consistent across kidney-function subgroups, with no significant interaction seen for the composite of CV death and heart-failure hospitalization (HHF) or for major adverse CV events.

"However, given their higher baseline risk, the magnitude of the absolute risk difference was significantly higher for participants with more markers of CKD (-0.5% for 0 markers, -1.0% for 1 marker, and -8.3%f or 2 markers; P = .02 for interaction for absolute risk difference)," the researchers report. "These findings suggest that 13 people with both eGFR lower than 60 mL/min/1.73m2 and UACR of at least 30 mg/g need to be treated for 4 years to prevent 1 event of the composite of CV death or HHF."

The researchers note that the numbers of amputations, cases of diabetic ketoacidosis, fractures, and major hypoglycaemic events were balanced or numerically lower with dapagliflozin compared with placebo for participants with an eGFR below 60 mL/min/1.73 m^2 and an UACR of 30 mg/g or higher.

Overall, concluded Zelniker, "These data indicate an apparent disconnect between cardiovascular efficacy and measures of glucose control and suggest that SGLT2i should be considered in patients with T2DM and chronic kidney disease for the reduction of cardiovascular events."

The trial was funded by AstraZeneca. Dr. Zelniker reports financial ties to the company.

"...efficacy of dapagliflozin was generally consistent across kidney-function subgroups, with no significant interaction seen for the composite of CV death and heart-failure hospitalisation (HHF) or for major adverse CV events."

Zelniker TA, Raz I, Mosenzon O, et al. Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol.* Published online April 14, 2021. doi:10.1001/jamacardio.2021.0660

Pancreatic Beta Cells Interact With Vagal Sensory Neurons

Work in viral tracing, immunohistochemistry and mouse models suggests pancreatic islets are densely innervated by sensory neurons, many of vagal origin, according to Florida-based researchers.

Destroying visceral sensory nerves is known to impact pancreatic islet function, glucose metabolism and diabetes onset, "but how islet endocrine cells interact with sensory neurons has not been studied," Dr. Madina Makhmutova et al. at the University of Miami Miller School of Medicine, in Florida, note in *Gastroenterology*.

"Because visceral sensory innervation is a crucial component of homeostatic regulatory circuits," they add, "there is a need to understand how islets signal to sensory fibres."

As Makhmutova told Reuters Health by email, "The emerging field of bioelectronic medicine (electroceuticals) expects one day to treat diabetes by stimulating the vagus nerve to coerce the pancreatic beta cell to secrete insulin. The mechanisms through which the pancreas and other inner organs communicate with the vagus nerve, however, are poorly understood."

"The emerging field of bioelectronic medicine (electroceuticals) expects one day to treat diabetes by stimulating the vagus nerve to coerce the pancreatic beta cell to secrete insulin."

The team hypothesized that pancreatic islets "use serotonin as a signaling molecule to communicate with the brain via vagal afferents."

To characterize the sensory innervation of the pancreas, the researchers first investigated the pancreatic distribution of the sensory neuronal marker substance P across mouse strains using immunohistochemistry. This was consistent across strains.

The team initially established that under normal physiological conditions, serotonin is produced and released from mouse pancreatic islets in a glucose-dependent manner and that serotonin activates axonal terminals in the pancreatic islet. These responses were blocked by a serotonin-5HT2-receptor antagonist.

They then established that vagal sensory neurons respond to serotonin secreted from activated beta cells. Neurons in the vagal nodose ganglion responded in vivo to chemogenetic stimulation of beta cells and to pancreas infusion with serotonin, but were not sensitive to insulin.

Vagal activation by islet serotonin, the researchers suggest, "informs the brain about how much insulin is secreted in normal physiology as well as about the functional adaptations of the islet to physiological challenges."

However, they note that such a role for serotonin is controversial, and it "thus remains to be determined if the mechanism described in this study translates to human beings."

Nevertheless, Makhmutova concluded, "Our study shows that insulin-secreting beta cells activate vagus sensory neurons that project to the brain. Although the physiological role of this neuronal connection remains to be defined, our findings suggest that vagus-nerve manipulation (either stimulation or blockade) might have an effect on insulin secretion and glucose metabolism."

Douglas D (2020). Pancreatic Beta Cells Interact With Vagal Sensory Neurons - Medscape Nurses,Nov 13, 2020.

Reporting on:

Makhmutova M (2020). Pancreatic β-Cells Communicate With Vagal Sensory Neurons. *Gastroenterology*. 160 (3): 875-888.E11. DOI: https://doi.org/10.1053/j.gastro.2020.10.034