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Endocrine disruptors: Effect on the intestinal microbiota as a cause of type 2 diabetes mellitus

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ABSTRACT

With lifestyles changes, chronic non-communicable diseases are the new pandemic of this century. This includes diabetes, that even if it exists a polygenic genetic predisposition, the effect of epigenetics is more relevant. Among the epigenetic conditions are endocrine disruptors, to which human being have high exposure in daily life, these can damage multiple organs such as the intestinal microbiota, generating toxicity and predisposing to development of the disease. The goal of the article is to discuss the mechanisms of endocrine disruptors that can affect our health, particularly in terms of the development of type 2 diabetes mellitus due to intestinal dysbiosis. Taking in to account that we are in permanent contact to these, directly or indirectly, substances such as pesticides, plastics, medications, sweeteners, among others can be taken as endocrine disruptors.

Introduction:

Type 2 diabetes mellitus (T2DM) is a multifactorial disease; From a genetic point of view, more than 650 variants involved have been described so far [1], however, beyond the genetic component, external factors have been described, such as emerging contaminants, substances responsible for the deterioration of health in humans and ecosystems [2]. With lifestyles changes and the increased demand for food, exposure to these substances has increased, since their use is frequent in mass food production systems, which in this way manage to satisfy the greater demand for food without this implying that it is of better quality. These exogenous biological and chemical substances, to which we are exposed on a daily basis through oral, inhaled or dermal consumption [2], are considered endocrine disruptors (ED), which not only have adverse effects on health but even on offspring. [3] . These disruptors come from various sources, many times we are not aware of them and as they are more resistant to decomposition they tend to accumulate in the environment in an even imperceptible way [4,5]. The problem is greater when regulatory entities do not exert sufficient control, making these new emerging contaminants a public health problem. More than 3,000 emerging contaminants have been described globally; they are present in plastics, artificial sweeteners, cleaning products, cosmetics, beverages, pesticides, and personal care products, among others [6]. They have an additive and cumulative effect, given that many are lipophilic, which is why once they enter the body they accumulate in adipose tissue. Its presence is so high that even in studies such as that of Miquel Porta [7] , it was documented that 85% of the participants had detectable levels of DE such as biphenols, DDE and DDT, since many of these contaminants are hydrophobic and highly resistant to degradation [8].

The accumulation of these substances affects processes such as genetic transcription and the interaction with intra- and extracellular receptors. At the endocrine level, they alter the synthesis, secretion and elimination of hormones, generating dysfunction in body tissues, thus altering metabolic functions that can lead to diabetes and obesity. among others [9].

Endocrine disruptors and DM2:

EDs at the pancreatic level are associated with beta cell dysfunction, defects in insulin secretion and, as a consequence, increased gluconeogenesis and oxidative damage. This has been associated, among other factors, with aberrant expression and activity of microRNAs [4]. Another mechanism associated with the development of T2DM due to EDs is insulin resistance that is triggered by systemic inflammation [9].

Among the associated DEs are polychlorinated biphenyls, organochlorines, pesticides, BPA and phthalates, among others [5,10] . Currently, the frequent use of pesticides has been associated with a greater risk of DM2, especially in populations close to the crops that use these substances, due to their contact in water and food. Aldrin, dieldrin and heptachlor, belonging to the group of organochlorines [11], as well as trichlorophenoxyacetic acid (dioxin), are the products that are associated with the greatest risk for the development of DM2, recently Gang and collaborators [12], documented in a meta-analysis that in subjects exposed to dioxin or similar contaminants the risk is 1.78 (95% CI = 1.37-2.31) and 1.95 (95% CI = 1.56-2.43) for women and men respectively. These have been shown to alter glucose metabolism, resulting in elevations in serum glucose and insulin concentrations.

Endocrine disruptors, microbiota and DM2:

The intestinal microbiota (IM) is an often forgotten organ, it includes all the microorganisms that reside permanently or temporarily in the gastrointestinal tract [13] , it is estimated that it is made up of approximately 10^9 to 10^{12} microorganisms, within these There are approximately one thousand different species of bacteria, for which approximately 5 million genes are needed for coding [14] . Its composition is variable, includes bacteria, viruses, fungi and protozoa and is affected by conditions such as gestational nutritional status, type of delivery, age, nutritional strategies, hygiene and the use of medications [15–17]. This will directly determine metabolic, immune, renal, cardiovascular and neurological states, among others.

One cause of alteration in the microbiota is exposure to exogenous environmental pollutants, in this case we speak of "intestinal microbiota toxicity", these exogenous chemicals are associated with functional damage, which includes changes in the metabolites of the bacteria, loss of bacterial diversity and changes in energy balance, all of this will lead to the production of pro-inflammatory metabolites that, among other consequences, are associated with diseases such as DM2 [18].

The development of T2DM has been associated with dysbiosis of the intestinal microbiota [19,20] . Interestingly, it has also been found that adequate nutritional strategies and supplementation with pre- and probiotics are a form of treatment for it [21,22].

Regarding the development of DM2, we know that it is associated with low-grade chronic inflammation and an altered immune response [23] , it has been suggested that one of the causes is intestinal dysbiosis, since these microorganisms can induce metabolic dysfunction and affect the barrier function of the intestinal epithelium. Retinoic acid-inducible gene I-like receptors (RLRs) function as pattern recognition receptors (PRRs), which are responsible for the body's first line of defense against pathogenic microorganisms [24]. Normally, commensal anaerobic bacteria in the intestine can attenuate the inflammatory response by regulating the p65 (RELA) subunit of NF- κB of the RLR signaling pathway; however, in the presence of intestinal dysbiosis this process is altered and is associated with development. of diseases such as diabetes.

Another inflammatory mechanism associated with intestinal dysbiosis is the alteration in the metabolism of tryptophan and its derivatives, since by binding to the aromatic hydrocarbon receptors located in the intestinal mucosa, they improve the intestinal epithelial barrier [25]. Particularly, indole and skatole have anti-inflammatory properties that, working together with short-chain fatty acids and secondary bile acids, reduce stress on the

intestinal epithelium and regulate differentiation pathways and immune cell function, with an antioxidant and anti-inflammatory effect. inflammatory [26].

On the other hand, Indole also has the ability to regulate the expression of glucagon-like peptide 1 (GLP1) [27], thereby stimulating insulin secretion by activating enteroendocrine L cells, regulating plasma levels of insulin and glucose.

Among the elements that can trigger the toxicity of the intestinal microbiota are xenobiotics such as medications, heavy metals, pesticides, microplastics and artificial sweeteners.

Medications are one of the most common endocrine disruptors, and among these, antibiotics are the more often used [28] . Their frequency is high due to their indiscriminate use, either due to a lack of regulation in their sale in some countries or due to incorrect prescription. Although there may be partial recovery of the previous flora after its suspension, the functional alteration of the microbiota may persist [29], and this has been associated with the development of DM2 [30]. Other medications associated with intestinal dysbiosis are non-steroidal anti-inflammatory drugs [31], although these have not shown an increased risk of diabetes [32].

Heavy metals, when they come into contact with bacteria, promote or attenuate their toxicity. Their interaction has been associated with changes in the frequency of specific bacterial species, such as Firmicutes and Proteobacteria, which play a crucial role in intestinal health [33]. It has been documented that arsenic, lead, nickel, cadmium, chromium and copper are associated with the development of DM2 [34].

Currently, the use of pesticides in agriculture is increasing and therefore their exposure and effect on human health has more impact [35]. Organophosphate pesticides such as amides and phosphoric acid are the most used; when they come into contact with the microbiota, they alter esterase and acetate activity, leading to gluconeogenesis and glucose intolerance [36]. In animal models with zebrafish, it was observed that For example, tris (1-chloro-2-propyl) phosphate (TCPP) and resorcinol bis (diphenyl phosphate) (RDP) induce intestinal microstructural damage and oxidative stress [37], which are currently used in the manufacture of foams., acrylics and resins among others.

Regarding Di phthalate, present in perfumes and flexible PVC products (shower curtains, garden hoses, diapers, catheters, gloves), in murine animal models the exposure showed alterations in the function of the maternal pancreatic islets and disorder in the glucose and lipid metabolism of offspring. Regarding the metagenome of the intestinal microbiota, there was dysbiosis in both the mother and the offspring, with transmission of the dominant microorganisms through vertical transmission [38]. In a case-control study, Yuxuan found a correlation between the concentrations of eleven phthalate metabolites and biomarkers of oxidative stress and T2DM in the blood. They found significantly positive associations for mono(2-ethylhexyl) phthalate (MEHP) and mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) with T2DM ($P < 0.001$), apparently due to a central role of the activated alpha receptor. by the peroxisome proliferator (PPARα) [39]. Duan and collaborators [40] also observed a correlation between these phthalate metabolites and the levels of fasting glucose and glycosylated hemoglobin, increasing the risk of developing DM2.

The micro and nanoplastics widely used today have toxic effects that put the ecosystem and our health at risk [41,42] . Plastic oligomers released from packaging material have been described to migrate into food. The human digestive system is unable to break it down and its presence alters the absorption of micro and macronutrients [43]. Studies in murine models have shown the relationship between its exposure and alteration in glucose metabolism, due to inhibition in hepatic SIRT1/IRS1/PI3K pathways [44] and by phosphorylation of AKT and FoxO1 [45]. It has been described, specifically in polystyrene microplastics, that at the intestinal level they affect structural integrity, genetic expression related to tight junctions and the intestinal microbiota, by generating dysbiosis, particularly due to high levels of prevotellaceae [46,47].

Artificial sweeteners, frequently used today, are used to replace energy-producing sugars and maintain sweet taste in a wide range of products, but there is controversy over their effects on appetite and endocrine responses in solid foods with added sugar. reduced or without added sugar since their benefit is not as good as it is thought [48] , currently they are added in an apparently safe way to foods, but many generate toxicity on the intestinal microbiota, however, this condition is not taken into consideration. and its use is increasing. Some of these, when metabolized by these bacteria, can even produce carcinogenic substances [49]. It has also been documented that, for example, the use of saccharin has shown changes in the composition and function of the microbiota, changes seen in the development of glucose intolerance. [50,51] . On the other hand, neotame has been shown to cause apoptosis of intestinal epithelial cells by eliminating small interfering RNA (siRNA) from T1R3 expression, producing an alteration of the barrier with greater leakage in the monolayer and a reduction in the expression of claudin 3 on the surface, dependent on the T1R3 pathway [52].

Analysis:

Current lifestyles changes imply new habits, among them in a nutritional level, we have had to sacrifice quality for quantity to meet the high demand of our population. In the quest to achieve this goal, we are being exposed to new substances directly or indirectly, xenobiotics, often in an imperceptible way, for example, through artificial sweeteners, antibiotics or in food production chains through pesticides, microplastics and heavy metals. There is growing evidence of the damage this can cause to human and ecosystem health. The review carried out describes the mechanisms through which these disruptors can generate toxicity in the intestinal microbiota, leading to dysbiosis, which is associated with the development of diseases such as type 2 diabetes mellitus. On the other hand, we must reinforce the importance of optimizing nutritional strategies, as well as the supplementation of pre- and probiotics that improve the intestinal microbiota,

given that, as Sastre and Wang et al showed in their studies, it is a way for the prevention and treatment of cardio-metabolic diseases such as diabetes.

Conclusion

Exposure to endocrine disruptors is an increasingly common situation that affects our health through direct and indirect contact. There is evidence of its importance in the development of metabolic diseases such as type 2 diabetes mellitus, one of the mechanisms involved is intestinal dysbiosis due to toxicity, regulatory entities should be encouraged about the importance of regulating its use, as well as stimulating the best gut microbiota health through nutritional strategies and supplements.

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