Int J BioMed Public Health. 2020; 3(3):95-102
10.22631/ijbmph.2020.222782.1155

International Journal
of
BioMedicine and Public Health
http://www.ijbmph.com

Review Article

Association of fetuin-A with the pathogenesis of metabolic diseases

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Reza Afrisham[1], Seyyed Mohammad Reza Hashemnia[1], Ziba Majidi[1], Sadegh Mozaffari[1], Mahmoud Vahidi*[2]

ARTICLE INFO

Article History:
Received 8 March 2020
Revised 28 March 2020
Accepted 18 June 2020

Keywords:
Fetuin-A
Obesity
Diabetes
Non-alcoholic fatty liver disease
Cancer

[1]Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [2]Department of Laboratory Sciences, Faculty of Paramedicine, AJA University of Medical Sciences, Tehran, Iran.
Correspondence:
Mahmoud Vahidi, Department of Laboratory Sciences, Faculty of Paramedicine, AJA University of Medical Sciences, Tehran, Iran.
Email: mahmoud.vahidi@gmail.com

ABSTRACT

Introduction: Fetuin-A is a glycoprotein that is synthesized by liver cells. Studies have shown that this hepatokine is linked to various metabolic disturbances such as obesity, and diabetes. Therefore, this study was designed to evaluate the role of fetuin-A in the pathogenesis of metabolic disturbances.

Methods: The present study was a review article. The terms of “fetuin-A”, “diabetes”, “obesity”, “chronic kidney disease (CKD)”, “cardiovascular disease (CVD)”, “non-alcoholic fatty liver disease (NAFLD)”, “cancer”, “bone metabolic diseases” and “metabolic disease” were used for searching of research papers in databases including Embase, Scopus, Web of Science, PubMed and Google Scholar. The literature search was limited to papers published up to November 2019.

Results: Fetuin-A could be involved in the pathogenesis of metabolic diseases such as obesity, diabetes, CKD, CVD, cancer, bone metabolic diseases, and NAFLD through various signaling pathways.

Conclusion: The results of the current study showed that fetuin-A could be involved in the pathogenesis of the metabolic disease. However, the study on these findings needs further research and a better understanding of these pathomechanism communications, which can be promising and helpful in preventing and better targeting metabolic disorders.

Introduction

Analogous to the myokines and adipokines, the hepatic proteins are named hepatokines (1, 2). Fetuin-A is a 64 kDa glycoprotein that is found in relatively high concentrations (100-1000 µg / ml) in human serum (3). This glycoprotein is also known in humans as alpha2-Heremans-Schmid glycoprotein (AHSG) (4). Fetuin-A is secreted from hepatocytes and is considered as hepatokine (4). Until recently, it was believed that the liver was the only major organ that secretes fetuin-A, but later it was found that adipocytes could also synthesize fetuin-A (5). The highest values of this hepatokine are observed in fetal blood that is synthesized in different tissues, accordingly, the name fetuin is applied (6). Epidemiological studies have consistently shown that increased levels of fetuin-A can be seen in obesity and obesity-related complications, such as type 2 diabetes mellitus (T2DM) (3), metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) (7).

Studies have also indicated that fetuin-A concentration was positively correlated to leptin concentration, visceral adipose tissue, and body mass index (BMI) (7). Moreover, circulating fetuin-A is higher in insulin-resistant obesity than insulin-sensitive obesity (7) so that, fetuin-A interferes with insulin signaling at the level of tyrosine kinase receptor (8) and lead to a higher risk of T2DM (3). Also, it has been established that the single nucleotide polymorphism (SNP) of the AHSG gene is associated with T2DM (7). Also, it has been reported that there is a positive correlation between fetuin-A levels and stage of liver fibrosis (7, 9). In cancers, in addition to the liver, cancer cells themselves also synthesize and release fetuin-A (10-12). Studies show that fetuin-A plays a role in enhancing cancer cell attachment (13), motility, and invasion (14, 15). Given the changes of fetuin-A in metabolic diseases; we aimed to evaluate the molecular and cellular mechanisms linking hepatokine fetuin-A to the pathogenesis of metabolic diseases.

Methods

The present study was a review article. The terms “fetuin-A”, “diabetes”, “obesity”, “chronic kidney disease”, “cardiovascular disease”, “non-alcoholic fatty liver disease”, “cancer”, “bone metabolic diseases” and “metabolic disease” were used for searching research papers in databases including Embase, Scopus, Web of Science, PubMed and Google Scholar. The literature search was limited to papers published up to November 2019.

Results

Association of fetuin-a with obesity

Obesity is a metabolic disorder that is considered as one of the important risk factors for CVD, NAFLD, and T2DM (6). Adipocytes in addition to hepatocytes could synthesize fetuin-A (5). Experimental and clinical studies have shown that fetuin-A has an obvious role in obesity (16). In 2017, Pérez-Sotelo et al. demonstrated that visceral adipose tissue more than subcutaneous adipose tissue secreted fetuin A that was sensitive to physiological and nutritional changes. They suggested that adipose-fetuin A played a key role in the deleterious effects of obesity (17). It has been established that leptin concentration, visceral adipose tissue, and BMI are positively correlated with serum fetuin-A concentrations (7). Positive energy balance in mice has been shown to increase fetuin-A mRNA expression levels (18). Besides, it has recently been shown that a positive energy balance in humans increases blood fetuin-A levels (19). After gastric bypass surgery along with a dramatic weight loss, a significant reduction in the levels of this hepatokine was observed (20).

It was very interesting that Mathews et al. indicated that when fetuin-A knockout mice fed a high-fat diet, a significant reduction of body fat , as well as resistance to the weight gain, was observed as compared to controls (21). In 2010, Dasgupta et al. showed that the incubation of HepG2 cells or mouse hepatocytes with palmitate stimulated NF-κB (nuclear factor-kB) binding to the fetuin-A promoter; leading to increased levels of mRNA expression, protein synthesis, and the secretion of fetuin-A (22). Jung et al. evaluated the influences and regulatory mechanisms of adiponectin and salsalate on fetuin-A expression in palmitate-induced HepG2 cells. Palmitate elevated SREBP-1c and fetuin-A expression and resulted in steatosis, while, knockdown of this hepatokine restored these changes. Adiponectin remarkably suppressed palmitate-stimulated fetuin-A mRNA expression and secretion through the adenosine monophosphate-activated protein kinase (AMPK) pathway. They concluded that adiponectin and salsalate improved impairment of lipid metabolism and palmitate-induced steatosis in HepG2 cells by the inhibition of this hepatokine through the AMPK-NFkB pathway (23). Thus, the decreased adiponectin, which is often seen in obesity (24), maybe another reason for the increase of fetuin-A in obese individuals (7). On the other hand, fetuin-A exacerbates this pathway and downregulates this adipokine in lipid-induced inflamed adipocytes (6).

Moreover, fatty acids stimulate fetuin A protein and gene expressions in adipocytes, leading to its copious release. Chatterjee et al. in 2013, showed that lipid-induced fetuin A from adipocytes acts as a chemoattractant factor for migration and polarization of macrophages which polarizes M2 macrophages to M1 (pro-inflammatory macrophages) (25). This hepatokine also induces secretion of pro-inflammatory cytokines such as IL-6 and TNF-alpha in adipose tissue (26). This inflammatory condition can contribute to the initiation and progression of other metabolic diseases, including insulin resistance, T2DM, NAFLD, CVD, and even cancer. Table 1 shows the association of fetuin-A with various metabolic diseases.

Table 1. Association of fetuin-A with various metabolic diseases

Studies	The metabolic disease	The involved tissue/cells/animal	Results
Pérez-Sotelo et al. (17)	Obesity	Adipose tissue	Visceral adipose tissue more than subcutaneous adipose tissue secreted fetuin A. This hepatokine played a key role in the deleterious effects of obesity
Mathews et al. (21)	Obesity	Fetuin-A knockout mice	Fetuin-A knockout mice fed a high-fat diet, a significant reduction of body fat as well as resistance to weight gain observed as compared to controls
Dasgupta et al. (22)	Obesity/NAFLD	Liver tissue	The incubation of HepG2 cells or mouse hepatocytes with palmitate stimulated NF-κB (nuclear factor-kB) binding to the fetuin-A promoter; leading to increased levels of mRNA expression, protein synthesis, and the secretion of fetuin-A
Jung et al. (23)	Obesity//NAFLD	Palmitate-induced HepG2	Adiponectin and salsalate improved impairment of lipid metabolism and palmitate-induced steatosis in HepG2 cells by the inhibition of this hepatokine through the AMPK-NFkB pathway
Chatterjee et al. (25)	Obesity	Immune cells	Lipid-induced fetuin-A from adipocytes acts as a chemoattractant factor for migration and polarization of macrophages which polarizes M2 macrophages to M1
Goustin et al. (31)	Diabetes	Mouse muscle cells	Human fetuin-A interferes with insulin receptor signaling at the level of tyrosine kinase. Fetuin-A inhibits insulin-stimulated GLUT4 translocation and activation of protein kinase B in mouse muscle cells and interferes with downstream phosphorylation of the insulin signaling pathway without affecting insulin binding to the alpha receptor subunit.
Zhao et al. (46)	Cardiovascular Disease	Serum	Subjects without CAD had significantly lower levels of serum fetuin-A
Akin et al. (47)	Cardiovascular Disease	Serum	Fetuin-A was significantly elevated in patients with CAD in comparison with patients without CAD
Chen et al. (34)	Cardiovascular Disease	Serum	Lower level of fetuin-A was related to an elevated risk of CVD and all-cause mortality in CAD patients.
Bilgir et al. (40)	Cardiovascular Disease	Serum	Fetuin-A was lower in myocardial infarction and stable angina patients as compared to control group
Naito et al. (49)	Cardiovascular Disease	Human umbilical vein endothelial cells *in vitro*	Fetuin-A induced the expression of intercellular adhesion molecule-1 (IAM-1), monocyte chemotactic protein-1 (MCP-1), E-selectin, and IL-6
Yusuf Yilmaz and et al. (9)	NAFLD	Serum	Serum level of Fetuin-A significantly increases in adult patients with NAFLD compared to healthy controls and a significant correlation was observed between serum Fetuin-A and liver fibrosis score index
Zhengsen Cui et al. (63)	NAFLD	Serum	fetuin-A in patients with NAFLD decreased when compared to healthy ones
Guillory et al. (76)	Cancer	Mouse	Lacking of fetuin-A reduces breast tumor incidence, extends latency, and decreases attenuation of aging caused by oncogenes. These events were triggered by an increased TGF-β signaling pathway and decreased phosphatidylinositol 3-kinase/Akt signaling pathway
Babler et al. (102)	Metabolic Bone Diseases	Mouse	The calcified soft tissues of mice lacking fetuin-A, after exposure to this glycoprotein, it returns to normal
Sari et al. (107)	Metabolic Bone Diseases	Serum	Fetuin-A levels are lower in postmenopausal osteoporotic patients than in controls
Caglar et al. (114)	Chronic Kidney Disease	Serum	In a group of nondiabetic subjects with different stages of CKD, fetuin-A levels diminished with a reduction in glomerular filtration rate
Coen et al. (115)	Chronic Kidney Disease	Serum	Hemodialysis patients with lowest tertile of fetuin-A had the maximum CRP levels
Mehrotra et al. (110)	Chronic Kidney Disease	Serum	The association between high levels of serum fetuin-A and decreased renal clearance and remarkable proteinuria in diabetic subjects

Association of fetuin-A with diabetes

T2DM is a chronic metabolic disorder that results from insulin resistance (27) and is considered as one of the important risk factors for CVD, and NAFLD (6). As mentioned above, fetuin-A has an obvious role in obesity (16). On the other hand, it has been reported that circulating fetuin-A is higher in insulin-resistant obesity than insulin-sensitive obesity (7). Also, it has shown that the risk of diabetes is higher in women and/or men with elevated concentrations of fetuin-A (3). Studies have shown subjects with T2DM had higher levels of hepatokine in comparison with nondiabetic individuals (26, 28, 29). Genetic studies observed that the SNP of the AHSG gene is associated with T2DM (7) as well as both known susceptibility loci for T2DM and the gene encoding this hepatokine are localized on chromosome 3q27 (30). In addition to this study, many studies have also shown that elevated fetuin-A levels can cause insulin resistance in liver cells (6, 8).

Some possible mechanisms might describe the relation between fetuin-A and T2DM. This glycoprotein is an endogenous inhibitor of the insulin receptor tyrosine kinase in muscle, fat, and liver tissue (8). In another study in 2013, Goustin et al. showed that human fetuin-A interferes with insulin receptor signaling at the level of tyrosine kinase. In fact, fetuin-A inhibits insulin-stimulated GLUT4 translocation and activation of protein kinase B in mouse muscle cells. This hepatokine also interferes with downstream phosphorylation of the insulin signaling pathway without affecting insulin binding to the alpha receptor subunit (31). Besides the direct effects of fetuin-A on the insulin receptor, it can also increase insulin resistance by inducing an inflammatory state. So that, treatment with fetuin-A increases the mRNA and protein expression of proinflammatory cytokines in both adipocytes and monocytes (7, 22). A recent study reported that fetuin-A is essential for non-esterified fatty acids to induce inflammation and insulin resistance through signaling Toll-like receptors (TLR4) in both adipocytes and macrophages (32). On the other hand, adiponectin is an adipokine with insulin-sensitizing and anti-inflammatory function that is reduced by fetuin-A (33) and the decreased adiponectin may be another mechanism for the fetuin-A induced insulin resistance.

Association of fetuin-A with cardiovascular disease

Obesity, T2DM, and NAFLD are the major risk factors for CVD (6). cardiovascular disorders are considered the leading reason for mortality worldwide (34). Fetuin-A serves a dual function in cardiovascular disorders (35), so that; a) high levels of this factor are correlated to metabolic disorders related to CVD including obesity, T2DM, insulin resistance, and NAFLD (3, 26, 35-38); b), it reduces the risk of CVD through the inhibition of vascular ectopic calcification (3, 39). This factor is reduced in individuals with acute myocardial infarction (40). Low levels of this hepatokine are correlated to higher mortality risk in a patient with coronary artery diseases (CAD) (34) and the severity of calcification (41-43). In contrast with these results, studies have shown that high levels of this hepatokine were correlated to the CVD conditions (44-46). Therefore, the association between this hepatokine and CVD is more controversial.

In 2013, Zhao et al. (46) evaluated fetuin-A serum levels in CAD patients with T2DM. They showed that subjects without CAD had significantly lower levels of serum fetuin-A as comparted to CAD patients. In addition, Akin et al. in 2015 studied the correlation of fetuin-A with CAD (47) as well as coronary plaque burden (48). This hepatokine was significantly elevated in patients with CAD in comparison with patients without CAD (47, 48). By contrast, Chen et al. 2017 (34) indicated that a lower level of this hepatokine was related to an elevated risk of CVD and all-cause mortality in CAD patients. Bilgir et al. (40) demonstrated that fetuin-A was lower in myocardial infarction and stable angina patients as compared to the control group. However, Naito et al. (49) showed that fetuin-A induced the expression of intercellular adhesion molecule-1 (IAM-1), monocyte chemotactic protein-1 (MCP-1), E-selectin, and IL-6 in human umbilical vein endothelial cells *in vitro*. In addition, this glycoprotein was abundantly expressed in cultured human monocytes, macrophages, human aortic smooth muscle cells, human coronary artery smooth muscle cells, fibroblasts, restenosis lesions in rat carotid arteries, and atheromatous plaques in human coronary arteries. This hepatokine stimulated collagen-1 and -3 expression and cell proliferation in human aortic smooth muscle cells as well as macrophage foam cell formation related to scavenger receptors (SR-A and CD36), acyl-CoA: cholesterol acyltransferase-1 down-regulation, and ATP-binding cassette transporter A1 up-regulation (49).

As mentioned above, fetuin-A induces inflammatory cytokines, C-reactive protein (50) as well as insulin resistance (32) that these factors play important roles in the development of CVD (51). On the other hand, many studies have shown the reduction of this hepatokine following exercise (52, 53). Since, the exercise decrease the risk factors for CVD (54-56); lower fetuin-A levels following exercise, can confirm high levels of this hepatokine in patients with CVD.

Association of fetuin-A with non-alcoholic fatty liver disease

NAFLD is a metabolic disorder related to fat accumulation which is observed in people who have no alcohol consumption. Today, to create this disease, the two-hit theory is proposed to introduce the first factor to insulin resistance and the next factor of oxidative stress (57). Secretory hepatokines of hepatic cells have a significant effect on glucose and lipid metabolism, which fetuin-A is one of these hepatokines. As mentioned, fetuin-A plays a role in most metabolic diseases such as obesity, insulin resistance, and cardiovascular events and can recognize it as a biomarker (58). Considering the importance of this marker and opposite findings, it is necessary to study it in liver disorders.

Fetuin-A is one of the hepatokines with negative metabolism functions. The increase of fetuin-A is observed in the circulation of patients with NAFLD and a positive correlation is found between fetuin-A levels and the stage of liver fibrosis (7, 9). Fetuin-A stimulates the production of pro-inflammatory cytokines and activates inflammatory signals through activation of TLR4. Accordingly, it can lead to NAFLD (59). Fetuin-A levels in people with impaired glucose tolerance were negatively correlated with insulin sensitivity and positively correlated with liver fat (36, 60). Toxicity of fat and glucose by stimulating ERK/1,2 and consequently increasing NF-KB, which results in increased fetuin-A upregulation causes hepatic steatosis (61). Fetuin-A in animal and human models plays a key role in insulin resistance (a risk factor for NAFLD) and acts as a phosphorylation inhibitor of insulin tyrosine kinase receptor in liver and skeletal muscles (62). The inhibition of this hepatokine could improve the impairment of lipid metabolism and palmitate-induced steatosis in liver cells through the AMPK-NFkB pathway (23).

In a study, Yusuf Yilmaz and et al. found that serum level of Fetuin-A significantly increases in adult patients with NAFLD compared to healthy controls and a significant correlation was observed between serum Fetuin-A and liver fibrosis score index (9). Conversely, in a study on the Chinese population by Zhengsen Cui et al., it was observed that fetuin-A in patients with NAFLD decreased when compared to healthy ones (63). To all appearances, Fetuin-A appears to be a marker for identifying different spectra of NAFLD and the link between diabetes and

NAFLD. However, given the contradictory findings of this hepatokine, it is important to study it further.

Association of fetuin-A with cancer

Since the genes of the metabolic pathways are out of regulation in cancer; it can be considered as the disease of metabolism (64-66). Numerous epidemiological studies have shown that certain types of cancers are more common in people with metabolic disorders (67). In cancers, in addition to the liver, cancer cells themselves also synthesize and release fetuin-A (10-12). Studies show that fetuin-A plays a role in enhancing cancer cell attachment (13), motility, and invasion (14, 15).

Fetuin-A induces cellular adhesion indirectly by regulating the secretion and stimulation of exosomes and their uptake by tumor cells (13, 68, 69). Fetuin-A has prometastatic activity and accelerates the process of colonization during calcium ion-dependent behavior (70). The Colonization process in organs is dedicated to an important part of cancer metastasis to yourself (71) and bone is a desirable place to attainment this process (72). Concerning the chemotaxis role for fetuin-A (14, 73), high affinity to hydroxyapatite crystals present in bone tissue (74), and protection of matrix metalloproteinases function (75); this biomolecule can be one of the important factors that make bone microenvironments tumor suitable for colonization of a variety of cancer cells .What is more, fetuin-A may be able to influential to determine the origin of metastatic traits in the latent and overt phases (71), as well as the severity and intensity of the colonization process (72). On balance, investigation of these ideas needs further research and a better understanding of these pathomechanism communications which can be promising and helpful in preventing and better targeting metastatic (especially latent) cancers.

Fetuin-A plays a significant role in the metabolic changes that affect cancer. In cancers that tumor initiation and progression are predominantly mediated by TGF-β signaling. Fetuin-A antagonizes this molecule during oncogenic transformation (76, 77). In 2010 Guillory et al. showed in mouse models the lacking of fetuin-A reduces breast tumor incidence, extends latency, and decreases attenuation of aging caused by oncogenes. These events were triggered by an increased TGF-β signaling pathway and decreased phosphatidylinositol 3-kinase/Akt signaling pathway (76). Concerning this problem, this question arises that is there a relationship between the production and accumulation of oncometabolite and fetuin-A (78-83). It may be possible to gain a deeper understanding of "how metabolic communication occurs in cancer" through this approach. Accordingly, it is also possible that modified forms of fetuin-A can be used soon for cancer diagnosis and staging (15).

Association of fetuin-A with metabolic bone diseases

In metabolic bone diseases such as osteoporosis, osteoporosis, osteomalacia, and rickets, the homeostasis and metabolism of calcium, phosphorus, and extracellular matrix are significantly affected (84-87). The rate of formation, the growth of hydroxyapatite crystals, and the degree of super-extracellular fluidization (serum) are influenced by several factors. Controlled regulation of these processes prevents ectopic mineralization or calcification in the physiological state (88, 89). Fetuin-A acts as a mineral chaperone (90) and due to the high affinity for the minerals (91), it can play a role in their muffling, buffering, and clearance (92-94).

Studies have shown that fetuin-A in this area has advantages compared to other proteins including 1) Despite its low circulating concentration, it has a more effective mineral-inhibiting capacity than other proteins, including albumin (91, 95, 96); 2) Compared to proteins such as osteopontin and dentin matrix protein-1 (DMP1), it fails to require phosphorylation for its inhibitory activity (91, 94, 97-99) and 3) It is the only protein that is not synthesized locally in calcified tissues (100, 101). Babler et al. showed that the calcified soft tissues of mice lacking fetuin-A, after exposure to this glycoprotein, it returns to normal (102). In the light of above mentioned it follows that fetuin-A has a greater effect on plasma calcium distribution than albumin and modifies calcium metabolism-related changes (which involves the connection of three skeletal reservoir, soft tissues, and extracellular fluid) to a larger scale.

Fetuin-A also inhibits the formation and growth of nascent hydroxyapatite crystals, as a result, it acts as a systemic inhibitor of ectopic mineralization (88, 94). By the same token, fetuin-A is considered as one of the factors of the anti-mineralization networks (103). The point is that this inhibition only occurs at the level of de novo synthesis (inhibition of osteogenesis) (94) and it is in the "formation" phase of the bone remodeling cycle (104). As a matter of fact, estrogen is the major regulator of bone metabolism in men and women (105) and the amount of fetuin-A was significantly increased by estradiol (106). In this connection, Sari et al. showed that fetuin A levels are lower in postmenopausal osteoporotic patients than in controls (107). One of the estrogenic strategies to prevent osteoporosis is to increase osteoclast apoptosis by stimulating transforming growth factor-β (TGF-β) production in the "formation" phase of the bone remodeling cycle (108). This process is synchronized with the action of fetuin-A at this phase; on the other hand, it is associated with the inhibition of TGF-β production by fetuin-A (83). It transpires that estrogen chooses special molecules to execute its functions strategy that needs further investigation to understand more deeply the therapeutic goals.

Association of fetuin-A with chronic kidney disease

Vascular calcification is a noticeable trait of chronic kidney disease (CKD) and a definite risk factor for cardiovascular events (61). Fetuin-A prevents precipitation of calcium and phosphate and acts as a potent systemic calcification suppressor (109, 110). Several studies reported an association between low levels of serum fetuin-A with vascular/valvular calcifications, and increased fatality in subjects with end-stage renal diseases (ESRD) (109, 111-113). Caglar et al. (114) elucidated that in a group of nondiabetic subjects with different stages of CKD, fetuin-A levels diminished with a reduction in glomerular filtration rate (GFR). Coen et al. stated that hemodialysis patients with the lowest tertile of fetuin-A had the maximum CRP levels (115).

Nevertheless, there were contradictory results in previous studies on the relationship between fetuin A levels and kidney dysfunction (109). Mehrotra et al. (110) showed the association between high levels of serum fetuin-A and decreased renal clearance and remarkable proteinuria in diabetic subjects. In other research on peritoneal dialysis patients, higher albumin was related to higher fetuin-A levels (116). However, given the contradictory findings of this hepatokine, it is important to study mechanisms linking fetuin-A to CKD further.

Conclusion

These findings indicate that fetuin-A through various signaling pathways could be involved in the pathogenesis of metabolic diseases such as obesity, diabetes, insulin resistance, inflammation, CKD, CVD, cancer, bone metabolic diseases, and NAFLD. The study on these findings needs further research and a better understanding of these pathomechanism communications, which can be promising and helpful in preventing and better targeting metabolic disorders. It transpires that fetuin-A chooses special molecules to execute its functions

strategy that needs further investigation to understand more deeply the therapeutic goals.

Ethical disclosure

Nothing to declare.

Acknowledgement

Nothing to declare.

Author contributions

All the authors contributed equally.

Conflict of interest

No conflict of interest has been declared by the authors.

Funding/support

No support funding.

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