



Review Article:

The Potential Role of Cholinesterase in Diabetes Mellitus and Metabolic Syndrome

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Abstract

Background: Diabetes mellitus is the most prevalent chronic disease in the world, that is deadly or severely lowers quality of life and affects females more than males. Persistent hyperglycemia and episodes of hypoglycemia contribute to systemic metabolic disturbances and a sustained low-grade inflammatory state, which plays a critical role in the pathogenesis of both type 1 and type 2 diabetes. Cholinesterase enzymes—acetylcholinesterase and butyrylcholinesterase—are involved in the degradation of acetylcholine, a neurotransmitter with anti-inflammatory and insulin-modulating properties. Recent evidence suggests a link between increased butyrylcholinesterase activity and systemic inflammation in diabetic and metabolic syndrome patients, highlighting its potential as a prognostic biomarker. **Aim:** to characterize and investigate the role of cholinesterase enzymes in predicting and monitoring the prognosis of diabetes mellitus as well as metabolic syndrome as its risk factor of such clinical condition. **Method:** Several excellent databases, including PubMed, Scopus, Web of Science, and Google Scholar databases, have been used in this review. These databases were selected due to their extensive coverage, search capabilities, and inclusion of reputable, peer-reviewed publications, which guarantee the accuracy and dependability of the data collected. **Results:** Studies show that butyrylcholinesterase activity is raised in both type 1 and type 2 diabetes and is linked to inflammation and metabolic syndrome. This enzyme correlates with worsening metabolic health, suggesting its potential as a marker for disease monitoring. **Conclusions:** Butyrylcholinesterase may serve as a useful biomarker for predicting and monitoring diabetes mellitus and metabolic syndrome, due to its role in inflammation and acetylcholine regulation.

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1. Introduction

1.1. Diabetes mellitus

Chronic hyperglycemia or diabetes mellitus (DM) is a metabolic condition brought on due to insufficient secretion of insulin or poor insulin action or both. Markedly, insulin is a crucial anabolic hormone, that influences how carbohydrates, lipids, and proteins are metabolized (1). The metabolic irregularities observed in DM mostly influence tissues like adipose tissue, skeletal muscles, and the liver due to insulin resistance (2). Various subtypes of diabetes exist, with type 1 and type 2 being the most dominant by far, accounting for nearly 5-10% and 90% of all cases, respectively (3). The harshness of symptoms can differ contingent with the length and sort

of diabetes. Individuals with extreme plasma glucose heights, chiefly individuals who are completely insulin deficient, like kids, may encounter symptoms like augmented hunger, polydipsia, dysuria, weight loss, and visual issues. Few public with DM may not feel any symptoms, particularly patients of the second type of DM in their initial stages (4). In line with the International Diabetes Federation's 2021 report (IDF), nearly 537 million subjects internationally lived with DM, establishing nearly 10.5% of the population of the earth, with the uppermost occurrence of undiagnosed DM seen in nations with low and moderate-income areas of Africa, the Western Pacific, and Southeast Asia (5,6).

As a result of developments in the care of DM and thus linked to better life expectancy, the way that diabetes complications manifest is evolving (7). While mortality from vascular problems is declining, which made up more than fifty percent of deaths in diabetic individuals (8), malignancy besides dementia currently are the leading causes of death in diabetic patients in a few nations or provinces (9-11). Moreover, research has shown a remarkable relation between DM and a wide series of comorbidities, including cognitive drop (12), functional

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disability (13), affective disorders (14), obstructive sleep apnea (15), and hepatic illness (16), what is more, had improved our awareness of the association among DM and infection see **Figure 1** (9,17).

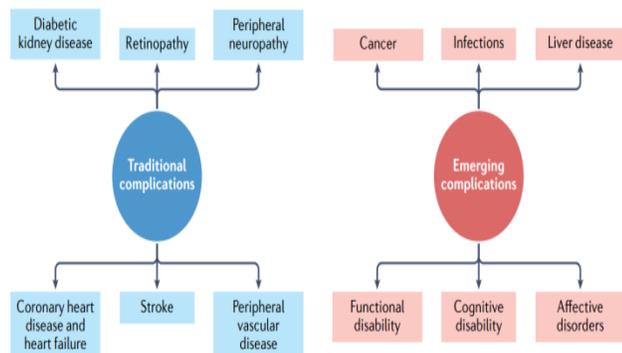


Figure 1. Major traditional complications as represented on the left-hand side of the diagram and emerging complications of diabetes mellitus as depicted in the right-hand side of the diagram. With advances in the management of diabetes mellitus, associations between diabetes mellitus and cancer, infections, functional and cognitive disability, liver disease and affective disorders are instead emerging (9).

Thus, early detection and handling of DM is critical and can avoid complications and support the dropping of severe well-being problems (18). However, limitations exist in diagnosing prediabetes, with different cutoffs for fasting glucose and HbA1c. Thus, other methods are needed to identify high-risk groups. Whereas most analytical challenges of HbA1c assays have been addressed, clinical challenges remain for HbA1c test use. Indeed, HbA1c results are not interpretable in a variety of specific situations like alteration of RBC turnover, thus necessitating adopting alternative approaches (19). In diabetes, the immune system and inflammation play key roles through both the development and progression of the ailment and correlated complications (20).

1.2. Metabolic syndrome

It is also acknowledged as insulin resistance syndrome, Reaven syndrome, or syndrome X; is a major international health concern. According to WHO it is a metabolic irregularity correlated with visceral adiposity. It involves glycolipid metabolism described by high systemic blood pressure, abdominal obesity, resistance to insulin & dyslipidemia (21,22). MetS is a pandemic-scale obesity-driven illness that raises the risk of cardiovascular disease and type 2 diabetes. Although inflammation has been linked to the etiology of MetS, the pathophysiological processes are not well understood (23).

2. Overview of cholinesterases

Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) are enzymes involved in adjusting the level hence the effect of ACh by its breakdown into choline and acetate ion(24). While AChE functions as a primary serine hydrolase, BChE is a nonspecific serine hydrolase capable of hydrolyzing broad choline-based esters (24). True cholinesterase (AChE) is found in the erythrocytes and central nervous system, while Pseudocholinesterase (BChE) primarily occurs in plasma and the liver (25).

Presynaptic neuronal cells and non-neuronal cells biosynthesize the neurotransmitter acetylcholine (ACh); T cells are primarily responsible for producing the neurotransmitter present in blood (26). Also, it is emphasized that inflammatory cells creating ACh are vulnerable to its effects (26). Borovikova et al proposed that vagal stimulation resulted in ACh release, which in turn operated on local inflammation, reducing the release of pro inflammatory cytokines thus concluding what is called “cholinergic anti-inflammatory pathway“ (27). Thus, ACh may alleviate inflammation, which will potentiate the important role of ChEs in DM (28). Because many studies highlighted the association between BChE and low-grade systemic inflammation(23,29–31), the present review aims to characterize and investigate the role of ChEs in predicting and monitoring the prognosis of DM as well as metabolic syndrome as its risk factor of such clinical condition.

3. Role of cholinesterase in the pathogenesis of DM

DM is the most prevalent chronic disease in the world, that is deadly or severely lowers quality of life and affects females more than males (32,33). Both type 1 and type 2 diabetes are characterized by inflammation, and chronic hyperglycemia and hypoglycemia episodes in DM lead to metabolic changes that promote an overall low-grade inflammatory state in the body (34). Many studies reported the association between ChEs and DM or its complications. If serum ChE activity was assessed in patients with DM, hypertension, and DM/hypertension in a study conducted in 2006 by Inacio Lunkes et al.. ChE activity was considerably lower in the control group than in the DM and hypertensive DM groups. Both the DM and DM/hypertensive groups had higher blood glucose levels. Only the control group had normal levels of TG and cholesterol. As a conclusion, in diabetic individuals, there is a correlation between increased serum cholinesterase and vascular problems, which may be triggered by levels of glycemia and dyslipidemia (35).

Patients with T2DM have increased BChE and AChE activities in their plasma and red blood cells (RBCs), according to Rao et al. (2007). This suggests that measuring these enzymes can help predict prognosis and response to treatment in type 2 diabetes. Additionally, their plasma levels may be accurate indicators of low-grade systemic inflammation (36).

Furthermore, even after controlling for variables like age, body mass index (BMI), fasting plasma glucose (FPG), Alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and triglyceride (TG), elevated serum BChEs were found to be independently associated with an increased risk of developing type 2 diabetes in the future in a prospective cohort study conducted in 2014 that included 8,470 Japanese men aged between 40–55 years who did not have T2DM at baseline. TG and HDL cholesterol did not affect the significance of this connection (37).

Mushtaq et al in 2014 showed that higher levels of the AChE and BChE are found in people with type 2DM (T2DM). Specifically, BChE activity is elevated in both type 1 and type 2 DM. This is important because BChE may contribute to T2DM by causing insulin resistance and increasing lipoprotein synthesis, thus proposed extra studies are required to fully realize the link between these enzymes & T2DM, but these findings suggested they could

be potential targets for future treatments (38). Moreover, Abdominal Obesity (AO) is linked to cardiovascular disease and type 2 T2DM investigated by Tangvarasittichai et al. in 2015. A study of 500 AO and 142 non-AO women found that AO subjects had higher BChE activity, insulin resistance, and a lower HDL-C level, potentially predicting the development of T2DM, which is mediated through insulin resistance (39).

A randomized double-blind clinical trial by Gholami et al. in 2019 aimed to evaluate the effects of Co-Q10 (a basic antioxidant for energy-making in mitochondria) supplementation on the blood levels of GGT, BChE, bilirubin, ferritin, high-sensitivity reactive protein, and metabolic syndrome biomarkers in female patients with T2DM revealed that after supplementation, blood levels of FBS, Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), BChE, TC, LDL-C, and ferritin were reduced, and levels of HDL-C were elevated in female with T2DM (40). However, a case-control comparative study in 2019 tested human plasma and erythrocyte ChE activity in five groups of diabetic patients with different levels of DM. Results, as recorded in Table 1, showed a relationship between BChE and diabetes, but no such relation with AChE. Dyslipidemia also affected both types of ChE enzymes. Inadequately controlled DM and dyslipidemia can cause elevation in both types of ChE enzymes, but less than dyslipidemia alone (41).

The effects of metformin and glibenclamide on the liver biochemical profile and AChE and BChE activities in two

groups of T2DM patients; group 1 was patients without nonalcoholic fatty liver disease NAFLD and group 2 was patients with NAFLD; were investigated in a case-control study conducted in 2021. The subjects in the control group appeared to be in good health. The activity of both enzymes (AChE & BChE) in both clusters 1&2 was notably different from the control, but far inferior in cluster 2 compared to cluster 1 and control. These results propose a possible caring effect of the drugs in diabetic-NAFLD patients demonstrated as dropped ChE activities (42). Another study conducted in 2022 examined the correlation between glutathione peroxidase (GPX) activity, BChE concentration, fasting blood glucose (FBG), and Lipoic acid synthetase (LIAS) levels in type 2 DM patients. Results showed higher FBG and HbA1c levels in diabetics, lower GPX activity, and increased BChE concentration compared to control, whereas LIAS concentration in the control was insignificantly increased compared to patients with diabetes, concluded that HbA1c, FBG, LIAS, BChE, and GPX are valuable biomarkers for disease monitoring and ought to be utilized in standard clinical diagnostic processes to assess patient clinical conditions (43).

More recently according to a community-based cohort study conducted in 2023 by Yu et al, 1133 participants with DM were analyzed to examine the association of ChE and the occurrence of diabetic retinopathy (DR). The results showed that ChE was linked to the occurrence of DR, particularly referable DR. ChE may be a possible marker for expecting the occurrence of DR (44).

Table 1. Clinical studies reporting serum BChE activity in DM

NO	Design / sample	BChE in DM	Principal finding	Ref.
1	Mixed-DM cohort; 73 DM, 25 controls	↑; linked to dyslipidemia and vascular risk	Elevated BChE associated with glycaemia & TG	(35)
2	Observational; 66 T2DM, 66 controls	↑ in plasma & RBC	proposed prognostic value	(36)
3	Prospective; 8470 normoglycemic men at baseline	↑ baseline BChE	Predicted incident T2DM, Risk independent of BMI & lipids	(37)
4	Review of T2DM cohorts	Consistently ↑; may drive insulin resistance	Both AChE & BChE implicated	(38)
5	Cross-sectional; 500 abdominally-obese women	↑ BChE	Associated with insulin resistance & low HDL-C	(39)
6	RCT; CoQ10 in T2DM women	↓ BChE	Improved metabolic profile after supplementation	(40)
7	Case-control; multiple DM groups	↑ BChE	Related to dyslipidemia; no AChE correlation	(41)
8	Case-control; DM with/without NAFLD	↓ BChE	Metformin & glibenclamide reduced enzyme levels	(42)
9	Cross-sectional; T2DM vs controls	↑ BChE	Correlated with HbA1c, FBG; lower GPX	(43)
10	Cohort; 1133 diabetic patients	↑ BChE	Linked to diabetic retinopathy, especially referable DR	(44)

4. Relationship between BChE and metabolic syndrome

Many studies, as reported in **Figure 2**, revealed an association between MetS or its components with elevated ChEs levels (45–47). Randell et al, (2005) measured the activity of serum BChEs along with MetS risk factors, in 1097 healthy subjects. The activity of Serum BChE was linked to the homeostasis of insulin and associated with levels of fasting insulin and insulin resistance (HOMA-IR) and was upper in patients having risk factors for MetS. Males showed higher BChE activity than females and showed the strongest correlation with serum level of triglyceride indicating abdominal obesity (48).

In 2007, another study by Iwasaki et al, involved two hundred fifty-nine individuals from Japan [one hundred seventy-one type 2 diabetic subjects (aging 60.4±11.9 years, BMI 25.0±4.4) and eighty-eight individuals free from diabetes (aging 54.2±15.0 years, BMI 25.8±4.7)]. Revealed that the activity of plasma BChE was considerably linked to different pointers of adiposity, involving the waist circumference, liver/spleen ratio, visceral fat area (VFA), subcutaneous fat area (SFA), and BMI, with Triglycerides, HDL-C, LDL-C, and HOMA-IR, in the whole individuals, indicating that the activity of plasma BChE was linked to adiposity factors, lipid profile, and IR (49). Once more, the role of BChE in metabolic syndrome is examined by Sridhar et al. (2010). According to the authors, BChE might be involved in the onset, manifestation, or progression of metabolic syndrome. The authors came to the conclusion that BChE has been demonstrated to interact at different degrees with distinct features of metabolic syndrome (50).

Furthermore, Stojanov et al in 2011 studied 1512 well non diseased individuals (aged 18–25 years). The study showed notable rise in BMI, TC, Triglyceride, LDL and albumin with BChE activity increment in males. Glucose and albumin increased with BChE activity in females. Also, a non-positive & not prominent association of BChE and HDL-C was noticed for both men and women. In conclusion, the propensity towards excess weight in young men might clarify the results on BMI as a self-determining risk factor for greater activity of BChE in young males. Glucose as a self-determining risk factor for greater activity of BChE in females, indicates that BChE can be a forecaster of DM (51).

Additionally, a randomized, double-blind, placebo-controlled trial was conducted in 2017 to evaluate effects of galantamine, an (AChE blocker) on inflammatory markers linked to insulin resistance and cardiovascular risk in individuals having MetS. Individuals with MetS were given galantamine eight milligrams by mouth every day for 1 month, followed by sixteen milligrams every day for 2 months, or a placebo. When compared to placebo, galantamine increased plasma concentrations of the anti-inflammatory molecules (adiponectin and IL-10) while decreasing concentrations of the proinflammatory molecules (TNF and leptin). Galantamine also markedly reduced HOMA-IR and plasma insulin levels. In conclusion, MetS patients who take low doses of galantamine experience less inflammation and insulin resistance (23).

After supplementing MetS patients with Chokeberry extract (which has antioxidant action), Duchnowicz et al. in 2018 highlighted a reduction in the activity of AChE in the RBC membrane, & also reported a decrease in total cholesterol, LDL-C, and TG levels and an increased levels of HDL-C along with reduced lipid peroxidation (52). Moreover, 1236 Chinese adolescents were involved in Han et al.'s (2019)

cross-sectional study [194 subjects with obesity (OB), 188 overweight (OW), 732 neutral weight (NW), and 122 underweight (UW)]. The study found that top layers of serum BChE concentration were connected to being overweight and also more strongly to being obese and validated a relationship between BChE concentrations and state of weight in Chinese teenagers. MetS and its components were strongly correlated with plasma BChE levels, which may help identify teenagers who have MetS (53).

A more recent study in 2021, a cross-sectional study that was matched by age and sex involved 54 prepuberale obese children (ages 6-9 years) and 54 nonobese children. Measurements were made of liver enzymes, soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6, C-reactive protein (CRP), adipokines, & Metabolic Syndrome-related markers. Children with obesity had significantly lower levels of apolipoprotein A-1, HDL-cholesterol, and adiponectin, and significantly higher levels of alanine aminotransferase (ALT), serum BChE, leptin, CRP, sICAM-1, TG, blood pressure, and HOMA-IR. These findings suggested that obese children had elevated levels of liver enzymes, leptin, insulin resistance markers, inflammation, endothelial dysfunction, & factors linked to Metabolic Syndrome (54). Moreover, studies about cholinesterase enzymes as a potential marker for metabolic diseases like diabetes mellitus and metabolic syndrome are not restricted to clinical studies alone but extended to involve animal studies too.

Table 2. Associations between serum BChE activity and metabolic syndrome

NO	Design	BChE Activity	Mechanistic explanation	Ref.
1	1097 healthy Canadians	Elevated	Higher in subjects with MetS risk factors; tracks insulin, HOMA-IR & TG—hepatic lipid-insulin resistance link	(48)
2	Cross-sectional, 259 Japanese (171 T2DM + 88 controls)	elevated	Correlated with visceral fat, lipid profile, insulin resistance—reflects adiposity-driven dysmetabolism	(49)
3	Narrative review	Elevated (overview)	BChE interacts at multiple levels with MetS traits; may drive syndrome progression	(50)
4	Cross-sectional, 1512 Serbian youths (18–25 y)	Elevated	BChE rises with BMI, TG, LDL-C in men and glucose in women—early risk indicator	(51, 52)
5	Cross-sectional, 1236 Chinese adolescents	Elevated	Higher BChE quartiles predict overweight/obesity and composite MetS score	(53)
6	Cross-sectional, 54 obese vs 54 non-obese children	Elevated	Elevation mirrors liver enzymes, leptin, CRP—links inflammation & endothelial dysfunction	(54)

5. Animal studies

In addition to what is mentioned above, numerous animal studies support the association between ChEs enzymes and DM (55,56). In a study conducted in 1975 assessing AChE activity in freeze-dried samples of rat pancreatic exocrine tissue and islets of Langerhans. Compared to exocrine tissue, islets had almost an order of magnitude more AChE activity. This variance in activity was seen in diabetic rats [made by streptozocin (STZ)] and in control. Even though diabetic rats' islets had on average 30–40% more enzyme activity than control rats, the changes were only statistically marginally significant. Cholinergic components linked to pancreatic islets are thought to be lost after STZ induces diabetes mellitus because the islets of diabetic rats are most likely significantly smaller than those of control rats (57) (Figure 2).

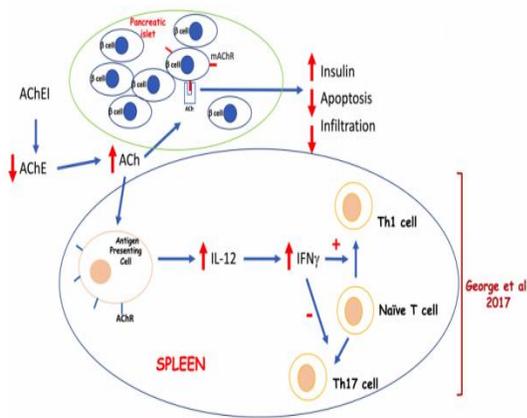


Figure 1. Suggested theory concerning the results of systemic inhibition of acetylcholinesterase on β cells of pancreas and lymphoid cells of spleen (28).

Serum BChE activity in addition to serum triglycerides, total low-density lipoprotein (TLDL), and glycerol rose in diabetic rats, according to a study conducted in 1991 that sought to determine the causes of the rise in serum BChE activity in DM. Implying that the liver's overproduction of very low-density lipoprotein was the cause of the elevated BChE activity. Serum glucose returned to normal after insulin treatment longest with the TLDL, triglycerides, glycerol, and BChE activity were all decreased. Administering a BChE inhibitor decreased serum triglyceride, TLDL, and glycerol in both diabetic and normal rats along with decreased activity of BChE (58). Tvarijonaviciute et al. in 2012 investigated the activity of serum BChE in diabetic dogs. The study showed that diabetic dogs had raised BChE levels as explained in human diabetics. Such raised activity might be related to the changes in the metabolism of sugar and lipids that happen in DM. More findings will be needed to explain the causes and outcomes of this finding for diabetic animals (59).

Many studies, as recorded in Table 3, highlighted the role of the cholinergic system in controlling metabolic abnormality through cholinergic anti-inflammatory pathway reflex (CAIR) (60). An essential homeostatic regulatory mechanism for detecting & managing the response of the body to inflammatory stimuli is the cholinergic anti-inflammatory reflex. Vago vagal reflexes

which are a basic part of CAIR, have anti-inflammatory actions that are provoked through activation of $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7nAChR$) on immune system cells via ACh. It has recently been recognized that $\alpha 7nAChR$ and CAIR also have a role in maintaining metabolic homeostasis. This has led to the perceiving that malfunctioning Vago vagal reflex circuitry underlying CAIR might clarify the co-existence of overweightness, chronic hyperglycemia, and inflammation in the MetS (60). According to another study in 2019 conducted in mice and rats, preganglionic Vagus Nerve (VN) efferent in these animals innervate ganglia of the pancreas where it forms connections with postganglionic neuronal cells which move to Langerhans (61). Acetylcholine liberated from these VNs efferent encourages β -cells to secrete more insulin (62). Additionally, in rats and mice, ACh was shown to have proliferative action on β -cell stimulating their copying thus increasing the mass of β -cells(63). In 2018 Gupta et al. conducted very conclusive research confirming that PNU 282987 which is agonist of $\alpha 7nAChR$ can prevent hyperglycemia, inhibit irreversible death of β -cell, and save the mass of β -cell by effect of β -cell pro-survival watched in model of diabetes in mice-the multiple low dose streptozotocin (MLDS)-model (64). The $\alpha 7nAChR$ agonist PNU 282987 supports the survival of pancreatic β -cells in stressful situations similar to diabetes by acting as a trophic factor (64).

Another study in 2022 aimed to assess the effects of GTS-21, (a selective alpha7 nicotinic acetylcholine receptor agonist), on diabetic nephropathy (DN) in -Leprdb/db mice, revealed that GTS-21 attenuated the development of DN in these mice, as evidenced by improved renal function, reduced inflammation, and decreased apoptosis. These findings suggest that GTS-21 may be a promising therapeutic agent for the treatment of DN (65). Furthermore, Meng et al. in 2022 looked to determine whether GTS-21, an $\alpha 7nAChR$ agonist, depresses blood glucose levels in db/db mice and whether this activity requires harmonized activation of the GLP-1 receptor (GLP-1R) by GTS-21 and endogenous GLP-1, respectively. The results showed that in db/db mice, $\alpha 7nAChR$ agonists enhance oral glucose tolerance. Coordination between GLP-1R and $\alpha 7nAChR$ activation is vital for this function. Therefore, $\alpha 7nAChR$ agonists combined with sitagliptin may be a novel treatment for T2DM (66). Additionally, many studies emphasized the critical importance of M3 subtype muscarinic cholinergic ACh receptors of Beta-cells in controlling the liberation of insulin and maintaining glycemic control and suggested a unique therapeutic plan to excite the action of these receptors to diminish the metabolic problems related to T2DM (Figure 3) (67–69).

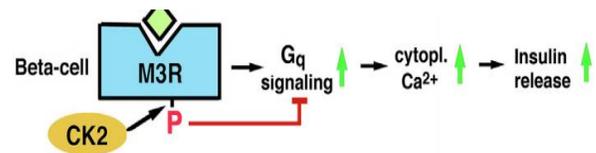


Figure 3. Beta-cell M3R agonist can trigger insulin release (69).

More recently a study conducted in 2023, examined how galantamine affected the development of DN in the db/db mice model, as well as intake of food, weight of body, and glycemic control. The conclusions afford proof that in the mice model, galantamine affects T2DM and DN via a variety of mechanisms, such as decreased intake of food and loss

of body weight., enhanced blood sugar control and sensitivity to insulin, and a decrease in systemic inflammation and renal apoptosis, partly through modifying p38 MAPK (mitogen-activated protein kinase)

and Caspase-1 pathway activity. More significantly, it offers proof that CAP can be used as a therapeutic target for T2DM and to prevent consequences such as diabetic nephropathy (70).

Table 3. Animal studies involving cholinesterase or cholinergic modulation

NO	Model / Intervention	BChE / AChE activity	Key outcome / mechanistic notes	Ref.
1	STZ-diabetic rats; islets vs exocrine	↑ AChE	Islets show ~10× higher AChE than exocrine tissue, diabetic rats show 30–40 % higher AChE vs control suggests cholinergic role in β-cells	(57)
2	STZ rats ± physostigmine	↑ BChE , (↓ with inhibitor)	Physostigmine lowered TG & BChE; partial metabolic rescue	(58)
3	Spontaneous diabetic dogs	↑ BChE ,	Raised BChE reflects glucose & lipid derangement	(59)
4	Non Obese Diabetic mice + galantamine	↓ AChE (pharmacologically)	AChE inhibition attenuates autoimmune diabetes via CAP	(55)
5	Non Obese Diabetic mice + cholinergic stimulation	Not measured	Cholinergic CAP prevents Th17-mediated diabetes	(56)
6	MLDS mice + α7nAChR agonist	Not measured	α7nAChR agonist preserves β-cell mass and euglycaemia	(64)
7	db/db mice + GTS-21	Not measured	Improved OGTT via α7nAChR-GLP-1 synergy	(65)
8	db/db mice + galantamine	↓ AChE (pharmacologically)	Galantamine reduces nephropathy & inflammation	(66)

6. A point of view

The integration of cholinergic signaling pathways through α7nAChR, M3R, and more general CAIR mechanisms, may knock on the door for managing DM and its consequences like DN. Targeting these pathways may open the door for multimodal treatments, and thus may improve Beta-cell survival (64), and insulin secretions (67,68), thereby glycemic control and inflammatory regulations (71). Agents like GTS-21, PNU 282987, and galantamine reveal the possibility of cholinergic remedies to minimize metabolic irregularities and their belongings, such as DN, in the running of both DM and MetS. Since many years ago till now, there have been ongoing studies on cholinesterases, and metabolic irregularities as reviewed above, highlighting a possible association between ChE and metabolic disorders with not completely understood mechanisms, suggesting more and more studies to establish a possible mechanism and emphasize such correlation. From my point of view, future-wise, ChE particularly BChE may play a vital role in the diagnosis, monitoring, prognosis, and management of diabetes mellitus and its related causes and complications.

7. Conclusion

In conclusion, ChEs, particularly BChE, are associated with DM and MetS. Various studies have shown that BChE activity is increased in both type 1 and type 2 diabetes, potentially contributing to insulin resistance and increased lipoprotein synthesis. Additionally, BChE is linked to the development, expression, and course of MetS. While the exact mechanisms and implications of this association are still under investigation, ChEs represent potential targets for future treatments and may serve as biomarkers for predicting and monitoring the prognosis of DM and MetS.

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الدور المحتمل لإنزيم الكولينستراز في داء السكري ومتلازمة التمثيل الغذائي

الخلاصة: يُعد داء السكري أكثر الأمراض المزمنة شيوعاً في العالم، وهو مرضٌ قاتل أو يُؤثر سلْباً على جودة الحياة، ويُصيب النساء أكثر من الرجال. يُساهم ارتفاع مستوى السكر في الدم بشكلٍ مُستمر ونوبات انخفاضه في حدوث اضطرابات أبطية جهازية وحالة التهابية مُزمنة منخفضة الدرجة، والتي تلعب دوراً حاسماً في نشأة كلٍ من النوع الأول والنوع الثاني من داء السكري. تُشارك إنزيمات الكولينستراز - أستيل كولينستراز وبوتيريل كولينستراز - في تحطيم الأستيل كولين، وهو ناقل عصبي ذو خصائص مُضادة للالتهاب ومُعدِّلة للأنسولين. تُشير الأدلة الحديثة إلى وجود صلة بين زيادة نشاط بوتيريل كولينستراز والالتهاب الجهازية لدى مرضى السكري ومتلازمة التمثيل الغذائي، مما يُبرز إمكانية استخدامه كعلامة حيوية للتنبؤ بمآل المرض. **الهدف:** توصيف ودراسة دور إنزيمات الكولينستراز في التنبؤ بمآل داء السكري ومتلازمة التمثيل الغذائي ومراقبته، بالإضافة إلى مراقبة مآل المرض باعتباره عامل خطر لهذه الحالة السريرية. **طرق العمل:** استُخدمت في هذه المراجعة عدة قواعد بيانات ممتازة، منها PubMed وScopus وWeb of Science وGoogle Scholar. وقد تم اختيار هذه القواعد نظراً لتغطيتها الشاملة، وقدرات البحث المتقدمة، واحتوائها على منشورات موثوقة ومحكمة من قبل النظراء، مما يضمن دقة البيانات المُجمعة وموثوقيتها. **النتائج:** تُشير الدراسات إلى ارتفاع نشاط إنزيم بوتيريل كولينستراز في كلٍ من النوع الأول والنوع الثاني من داء السكري، وارتباطه بالالتهاب ومتلازمة التمثيل الغذائي. ويرتبط هذا الإنزيم بتدهور الصحة الأبطية، مما يُشير إلى إمكانية استخدامه كعلامة حيوية لمراقبة المرض. **الاستنتاج:** قد يُستخدم إنزيم بوتيريل كولينستراز كعلامة حيوية مفيدة للتنبؤ بداء السكري ومتلازمة التمثيل الغذائي ومراقبتهم، نظراً لدوره في الالتهاب وتنظيم الأستيل كولين.

الكلمات المفتاحية: داء السكري، متلازمة الأبط، كولينستراز، أستيل كولينستراز، بوتيريل كولينستراز، التهاب