J Cachexia Sarcopenia Muscle (2013) 4:31–39
DOI 10.1007/s13539-012-0083-5

REVIEW

Butyrylcholinesterase as a prognostic marker: a review of the literature

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Received: 11 April 2012 / Accepted: 24 July 2012 / Published online: 6 September 2012

Abstract
Background Butyrylcholinesterase (BChE) is an α-glycoprotein synthesized in the liver. Its serum level decreases in many clinical conditions such as acute and chronic liver damage, inflammation, injury and infections, and malnutrition.
Methods and results This review collects the main evidence on the emerging role of butyrylcholinesterase as a prognostic marker of liver and nonliver diseases as well as a marker of protein-energy malnutrition and obesity. In fact, serum concentrations and BChE activity seem to accurately reflect the availability of amino acidic substrates and/or derangement in protein synthesis due to hepatocellular damage. In cancer, with or without liver impairment, serum BChE levels serve as an accurate functional and prognostic indicator, useful for monitoring clinical and therapeutic interventions according to patients' prognosis. In the absence of inflammation, BChE could also serve as an index of the effectiveness of nutritional support.
Conclusions Serum BChE assessment should be included in routine clinical diagnostic procedures to evaluate patient clinical conditions, in particular in cases of inflammation and/or protein-energy malnutrition.

Keywords Butyrylcholinesterase · Prognostic marker · Liver and nonliver diseases · Protein-energy malnutrition · Obesity

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1 Introduction

1.1 What is butyrylcholinesterase?

Cholinesterase represents a group of enzymes that hydrolyze acetylcholine and other choline esters. There are two main types of cholinesterase with different biochemical properties: true or specific cholinesterase or acetylcholinesterase found in all excitable tissues (central and peripheral nervous system and muscles) and in erythrocytes. It is a high-turnover enzyme with high affinity for acetylcholine, inhibited at high concentrations of acetylcholine, and with low affinity for noncholine esters [1].

The other one is the nonspecific or pseudocholinesterase or serum cholinesterase or butyrylcholinesterase which hydrolyses both choline and aliphatic esters. Butyrylcholinesterase (BChE) is an α-glycoprotein found in the central and peripheral nervous system, in most tissues, and in the liver. It has lower affinity for acetylcholine and is not inhibited by high concentrations of acetylcholine [1]. BChE half-life is about 12 days [2, 3], and its normal value ranges between 5,900 and 13,200 IU/L. An increased activity of this enzyme has been reported in obesity, diabetes, uremia, hyperthyroidism, and in hyperlipidemic subjects [4–6].

A small proportion of healthy population is lacking in plasma BChE, due to a genotype aberration; studies carried out in Europe indicate a 3–4 % prevalence of congenital serum BChE deficiency [7]. BChE is synthesized in the liver: a hepatocellular impairment will reflect a decreased enzyme activity. In fact, plasma levels fall in acute and chronic liver damage, cirrhosis, and liver metastases, being a biochemical marker of organ damage. Low plasma BChE levels have also been found in protein-energy malnutrition, during stress and (chronic and acute) inflammation, and in other clinical conditions [8]. On the other hand, plasma BChE activity was significantly elevated in both type 1 and 2 diabetes, compared

with the control subjects. In addition, BChE activity was positively associated with serum concentrations of cholesterol and triglycerides and with measures of overweight, obesity, and body fat distribution [9, 10].

2 Aim of the review

There are few and not updated data in literature on the significance of BChE variations according to some physiological and pathological conditions, but also according to our clinical experience, BChE seems to have a prognostic role in different diseases. As it will be described in the text, the prognostic value of BChE varies from disease to disease, being of outcome, discharge, survival, weaning off artificial nutrition, and disease progression.

The review aims to collect the main, past, and recent evidences reported in the literature on the emerging role of BChE as a prognostic marker in some liver and nonliver diseases, as well as in protein-energy malnutrition and obesity (Table 1).

3 Protein-energy malnutrition and inflammation

Protein-energy malnutrition (PEM) may have important adverse effects on clinical outcomes; for this reason, nutritional assessment should regularly be part of diagnostic procedures in acute and chronic diseases. Recent evidence suggests that either acute or chronic inflammatory diseases are key contributing factors in the pathophysiology of PEM.

In clinical practice, nutritional status may be compromised in conditions of (1) pure chronic starvation without inflammation (e.g., clinical conditions such as anorexia nervosa), (2) chronic diseases or conditions that impose sustained inflammation of a mild to moderate degree (e.g., organ failure, inflammatory bowel diseases, rheumatoid arthritis, advanced cancer, etc,), and (3) acute disease or injury states with marked inflammatory response (e.g., major infection, burns, trauma, or closed head injury) [11]. On the other hand, stress and inflammation can influence appetite and gastrointestinal motility, promoting through anorexia the vicious cycle: chronic–acute disease and PEM [12].

As well known, critical illness or injury promotes an inflammatory response that has a rapid, catabolic effect on fat-free (or lean) body mass. On the other hand, loss of muscle mass and function may insidiously occur, and in the chronic disease state, even over months to years. The presence of inflammation often limits the effectiveness of nutritional interventions while the associated malnutrition may compromise the clinical response to medical therapy. The anorexic patient and/or chronic disease-related malnutrition is prone to quickly deteriorate with any additional acute inflammatory event and warrants close follow-up.

"Positive" acute-phase proteins, such as C-reactive protein (CRP), directly rise with inflammatory disease activity; "negative" acute-phase proteins (albumin, prealbumin, and transferrin) inversely respond: their circulating levels decrease in response to injury and inflammation and increase during the recovery phase [13, 14]. These proteins reflect either cytokine-induced stress, catabolism, and anorexia, which in turn affect patient's clinical conditions and nutritional status. Therefore, the evaluation and monitoring of the preexisting inflammatory status appears crucial.

For its short half-life, some authors speculate on the usefulness of serum BChE as a nutritional and prognostic marker, rapidly changing with general clinical conditions and nutritional status [1]. BChE levels are strongly influenced by inflammation, sensitively decreasing in the acute inflammatory phase and promptly increasing when inflammation improves [15]. Serum BChE was already known to decrease in patients with PEM, probably due to inadequate availability of substrates for its synthesis rather than to hepatocellular failure [1].

In malnourished children with marasmus and edematous undernutrition (or kwashiorkor), serum BChE, total proteins, and albumin levels are lower than those measured in normal children; these values tend to increase after 3 weeks of nutritional rehabilitation [16]. In a similar study on 200 malnourished infants, the degree of edema resulted to be inversely related to BChE and albumin levels; a similar trend of serum BChE values was observed in undernourished adults [17].

In hospitalized patients diagnosed with protein-energy visceral or nonvisceral undernutrition, BChE levels resulted low and significantly correlated with transferrin, albumin, and cholesterol, particularly in visceral malnutrition. Visceral undernutrition is a condition strictly linked with low values of visceral proteins such as albumin, transferrin, and total lymphocyte count [18].

In conclusion, BChE levels seem to strictly correlate with the outcome of malnourished patients, being low during the inflammatory phases, in the case of inadequate availability of substrates, or in the presence of edema and recovering with the amelioration or resolution of these conditions. In particular, in case of malnutrition, BChE activity seems a reliable indicator of patient conditions, better than albumin, for the latter is more strongly influenced by inflammation.

3.1 Geriatric

As regard to the healthy geriatric population, no correlation has been found between BChE levels and advanced age, suggesting that age per se does not seem to be associated with reductions in esterase enzyme activity. This finding is particularly useful if we consider that the older population is frequently under medical treatments and that esterases are primarily involved in drug metabolism [19].

Table 1 Serum BChE levels in different physiological and pathological conditions

Clinical condition	Subgroups	BChE levels	Comments	Ref. no.
PEM and inflammation	Marasma/kwashiorkor	↓	BChE levels increased after nutritional rehabilitation	[16, 17]
	Hospitalization	↓	BChE levels low and significantly correlated with transferrin, albumin, and cholesterol	[18]
	Healthy geriatric population		Age does not seem to be associated with reductions in BChE activity	[19]
	Frail older people/acute illness	↓	BChE inversely related with cytokines IL-6 and TNF-α	[15]
Malignancy	Advanced cancer patients with or without liver involvement	↓	PChE predictive of survival together with albumin and Karnofsky index	[24]
	Hospitalized cancer patients	↓	BChE levels <1,900 IU/L related with negative prognostic outcome	[25]
	Cancer patients during nutritional support	↑		[27]
	Pancreatic cancer (75 patients)	↓	Low BChE levels represent a poor prognostic index	[29]
Hemodialysis	Chronically uremic patients	↓	BChE inversely related with IL-6 levels	[30]
Inflammatory bowel disease	Patients with Crohn disease	↓	BChE marker of PEM and inflammation	[33]
Critical illness	In severely burnt and critically ill patients with sepsis	↓		[33, 34]
	In patients receiving necessity OLT		Serum BChE levels are predictors of survival	[36]
Anorexia nervosa	97 AN patients and 66 ED-NOS	↓		[38]
Enteral and parenteral nutrition	Catheter-related infection	↓	Serum BChE strictly correlated with serum albumin, increase with the resolution of infection and TPN restoration	[41]
	Before starting PN/EN (312 patient)	↓	Low serum BChE levels related with negative outcome[a]	[40]
Liver and nonliver disease[b]	Hepatocellular impairment	↓↓		[23]
	Nonliver disease	↓		[23]
AIDS	AIDS patients with abnormal D-xylose test (malabsorption)	↓		[46]
HELLP syndrome	Pregnant women with HELLP syndrome	↓		[47, 48]
Obesity and metabolic syndrome	Myocardial infarction	↓	BChE levels inversely related to CV mortality	[50, 51]
	Protein content in the diet	↑		[54]
	Dyslipidemic insulin-treated type 2 diabetes	↑	Serum BChE activity positively correlated with serum triacylglycerol concentrations and decreased as a result of bezafibrate treatment	[55]
			Serum BChE correlated with fasting insulin levels, HOMA-R, C-peptide	[49]
	Low caloric diet in obese patients with fatty liver	↓	BChE activity decreased in parallel with improvement of hepatic steatosis	[69]
	High cardiovascular mortality rate	↓↓	Probable *BChE 1–2 gene* variants	[56]

[a] Negative outcomes' mean: death or interruption of parenteral/enteral nutrition, due to the worsening of clinical conditions

[b] Conditions where the traditional liver function tests may result abnormal without liver dysfunction (heart, muscle and bone diseases, increased erythrocyte breakdown, hypoalbuminemia due to nephritic syndrome, or protein-loosing entheropathy)

BChE has also been considered as a useful biomarker for the diagnosis and monitoring of malnutrition and in general as a prognostic indicator in the elderly [20, 21]. In literature, plasma esterases were found to decrease in frail older people and during acute illness: in 30 elderly patients, with increasing patient frailty, CRP, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) significantly increased, while BChE activity significantly dropped ($p<0.005$). In addition, BChE activity resulted to be significantly and negatively correlated with the proinflammatory cytokines IL-6 and TNF-α [18]. Also, in geriatric patients, BChE is a valid prognostic indicator, strictly related with nutritional status and inflammation.

3.2 Malignancy

Advanced cancer is a condition in which mild to moderate inflammation is frequent and interacts with various degree of PEM. Plasma BChE levels resulted to be decreased in advanced cancer patients, with or without hepatic involvement: the lowest activity has been found in patients with hepatic metastases, despite the normality of other liver function tests [22]. One of the possible mechanisms responsible for BChE activity decrease in cancer patients could be secondary anorexia accompanying malignancy [23].

In a study by our group in 152 terminal cancer patients with peritoneal carcinosis, BChE serum levels resulted to be a survival predictive factor together with albumin and Karnofsky index [24]. In 126 hospitalized cancer patients, undergoing a nutritional assessment at admission and after 1 week, it was observed that, in case of a serum BChE level below 1,900 IU/L at entry, the risk of developing relevant weight loss, hypoproteinemia, and hypoalbuminemia during hospitalization resulted to be significantly higher [25]. In another study of patients with head and neck or uterine cervix cancer who are in radiation therapy, BChE activity showed to be an affective prognostic marker: BChE activity resulted to be lower in all patients before starting radiation therapy, increased as radiotherapy progressed, and remained in the normal range at 6 months of follow-up in those patients with no detectable disease activity [26].

Bozzetti et al. observed that serum BChE, rapid turnover proteins (transferrin, thyroxin-binding prealbumin, and retinol-binding protein), body weight, and nitrogen balance improved during nutritional support in cancer patients. According to recent evidences, in these conditions too, the improvement of serum proteins levels, more than a specific nutritional recovery, could primarily reflect the reduced inflammation and the improvement of general clinical conditions [27].

In stress conditions, such as cancer cachexia, there are metabolic derangements where synthesis and catabolism are both higher than in unstressed malnourished patients or in fasted normal volunteers. In 246 patients with non-Hodgkin's lymphoma, the same authors wondered about a possible relationship between nutritional status (weight, weight loss, albumin, BChE activity, lymphocyte count) and tumor growth (evaluated with the rate of incorporation of ^{3}H-labeled thymidine in the tumor tissue). The only significant association was found between low serum BChE activity (index of a poor nutritional status and presence of inflammation) and high incorporation of ^{3}H-labeled thymidine, demonstrating also that the maintenance of a good nutritional status has no deleterious effect on tumor growth [28]. Finally, in 75 patients who underwent macroscopic curative resection for pancreatic cancer, low serum BChE levels correlated with nerve plexus invasion of the primary tumor, thus representing a poor prognostic index. Patients with low serum BChE levels also manifested systemic disorders, including poor performance status, anemia, and hypoalbuminemia [29]. In patients with cancer, BChE levels seem to correlate with disease activity and nutritional status and could represent a valid survival predictive factor.

3.3 Hemodialysis

Uremic patients undergoing hemodialysis are often catabolic and malnourished; they commonly feed on inadequate quantities of protein and calories and may be protein-depleted, with a mixed marasmus/kwashiorkor-like pattern of protein-energy malnutrition. Malnutrition in uremia can be affected by many factors: uremic toxicity, infections, hypercatabolism, loss of amino acids during dialysis, abnormalities in amino acid and protein metabolism, and decreased protein synthesis in liver. Also, in patients on chronic hemodialysis, BChE was used as prognostic marker, in addition to the other traditional parameters (anthropometric indices, serum protein content, immune response indexes) [30, 31]. Serum protein, albumin, C3, blood lymphocyte count, and BChE generally resulted to be decreased in chronically uremic patients undergoing conservative or dialysis treatments [30]. The short-term intravenous supplementation of essential amino acids during dialysis determined a significant ($p<0.05$) increase in body weight, arm muscle circumference, and serum albumin as well as BChE levels.

The circulating levels of IL-6, a proinflammatory cytokine inducing the production of acute-phase proteins and involved in weight loss, resulted to be significantly higher in patients undergoing hemodialysis than in healthy volunteers and significantly and inversely related with serum albumin ($r=-0.4$, $p=0.006$) and BChE ($r=-0.51$, $p=0.001$) levels [31]. Patients in dialysis have a condition of chronic inflammation and malnutrition. Also, in this case, BChE is directly related with albumin and inversely related with inflammation.

3.4 Inflammatory bowel disease

As previously discussed, in acute inflammatory diseases, both serum BChE and albumin appeared to be inversely related with acute-phase proteins, due to the action of proinflammatory

cytokines [32]. Together with serum albumin concentration, BChE levels were also proposed as direct markers of malnutrition and indirect index of inflammatory activity in Crohn's disease (CD). In fact, BChE activity and albumin concentration resulted to be significantly lower in patients with active CD than in those with quiescent disease ($p < 0.001$), and both proteins were significantly lower in malnourished than in well-nourished patients [33].

3.5 Critically ill patients

In severely burnt patients and in critically ill patients, the absorption of nutrients in the upper regions of the intestine resulted to be slightly impaired for gastrointestinal dysmotility; serum BChE activity was found to be also decreased, suggesting subnormal biosynthetic processes [34]. In septic patients, serum levels of albumin, cholesterol, and (BChE) resulted to be significantly lower than in the control group [35].

In 133 consecutive adult patients receiving necessity orthotopic liver transplantation (OLT), predictors of 12-month mortality included lower BChE levels (2,900± 1.880 versus 3,700±2.020 IU/L, $p=0.026$). According to score-based medical urgency criteria pre-OLT, BChE is a predictor of short-term post-OLT survival and may be helpful as a bedside score in pre-OLT clinical management, outcome prediction, and decision making [36].

3.6 Anorexia nervosa

Anorexia nervosa (AN) represents a pure form of marasmus-like malnutrition. In AN, despite the occurrence of adaptive metabolic mechanisms due to chronic underfeeding, many organs and systems can negatively be affected. Regarding liver function, available evidences suggest that abnormalities in serum liver enzymes may occur and some cases of acute liver failure have been described. In AN, a mild to moderate increase in liver enzymes is expected to reflect a fatty liver, which is typical of several protein-energy malnutrition states. In these clinical circumstances, hepatic steatosis, among others, could have been the consequence of an imbalance between hepatic triacylglycerol synthesis and secretion and decreased lipoprotein synthesis, due to decreased amino acid availability [37]. Abnormal serum concentrations of BChE and other liver enzymes have frequently been found, not only in the severe cases of hospitalized AN patients but also in outpatients with either AN or eating disorder not otherwise specified (ED-NOS). Low BChE activity was observed by our group in 97 underweight outpatients with AN and in 66 with ED-NOS when compared with 56 controls; these results have been interpreted as a marker of the effects of primary malnutrition on liver function and lack of protein substrates.

In two extreme cases of AN, patients developed severe and acute liver failure with a marked increase of serum transaminases and a dramatic reduction of BChE levels. Following nutritional recovery, BChE rapidly increased [38].

In conclusion, in this study, low serum BChE activity has been reported in AN, independent of the age, weight, or BMI of patients, thus suggesting a predominant causal role for decreased nutrient availability rather than a relationship with changes in body composition [39].

3.7 Enteral and parenteral nutrition

Enteral and parenteral nutrition are medical therapies, often lifesaving for home and hospitalized patients. Together with other anthropometric, biochemical (serum albumin, prealbumin, transferrin, cholesterol, thyroxine-binding protein, retinol-binding protein) and hematological (lymphocyte count) parameters, serum BChE also appears to be a potential reliable prognostic marker, rapidly and sensitively changing with the variations of the patient's nutritional status and general clinical conditions [40].

In four patients on long-term home total parenteral nutrition (TPN), hospitalized in our clinical ward for catheter-related bloodstream infection, the septic state and TPN interruption, even when partially replaced by peripheral parenteral nutrition, induced a fast deterioration of the patient's general clinical conditions. In all patients, decreased blood levels of prealbumin, albumin, cholesterol, lymphocyte count, and BChE levels were observed. In the same patients, after the resolution of infection and TPN restoration, BChE levels promptly and sensitively increased (from +54.3 up to +124.8 %).

In these case reports, serum BChE represents a useful and sensitive marker of the amelioration of patient's clinical conditions after the resolution of infection and the restoration of TPN through the central venous catheter. Moreover, in these four patients, a close correlation between serum BChE and albumin was found [41]. The same correlation was found in 17 seriously ill surgical patients who received TPN for 4–21 days [42].

In a retrospective examination of 312 clinical records of patients before undergoing enteral and parenteral nutrition, Donini et al. found that the percentage of negative outcomes (death or interruption of parenteral/enteral nutrition, due to the worsening of clinical conditions) was higher in subjects >80 years of age, with higher comorbidities; reduced levels of albumin, prealbumin, lymphocyte count, and BChE; and higher levels of C-reactive protein [40].

Similarly to prealbumin, whose half-life is much shorter than albumin (2–3 versus 21 days), BChE serum levels are not only reduced by malnutrition but also by inflammation and liver diseases and resulted to be significantly correlated with negative outcome [43].

4 Liver and nonliver diseases

Regarding liver diseases, a decreased BChE activity reflects a hepatocellular impairment; similarly, recovery was evidenced by a gradual increase of BChE levels. During and after treatment with high dose interferon alpha performed in 101 patients with chronic HCV infection, total cholesterol levels gradually increased reaching normal values in responders. Serum BChE activity pattern paralleled that of serum cholesterol and was related with serum albumin, as already seen in chronic liver diseases [1, 44].

Serum BChE levels decrease in liver dysfunction as a consequence of reduced synthesis, in comparison with other liver enzymes whose levels increase because of an increased release from damaged cell membranes. The traditional liver function tests may result abnormal in other diseases, not related with liver dysfunction. For example, high level of serum transaminases can be the consequence of their release by nonliver tissues (i.e., heart and muscles); the increase of the serum alkaline phosphatase activity may result from physiological or pathological enzyme production from nonliver tissue (i.e., bone and placenta). In addition, serum bilirubin may rise because of increased erythrocyte breakdown and reduced albumin concentration due to increased renal or intestinal loss (i.e., nephrotic syndrome or protein-loosing entheropathy) [45].

Ogunkeye et al. evaluated if serum BChE activity could help in differentiating between liver and nonliver diseases in three groups of subjects: group 1, liver disease with at least four out of five abnormal liver function tests (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, total bilirubin, and albumin); group 2, nonliver disease with at least two abnormal liver function tests, and group 3, healthy subjects. Group 2 patients presented serum BChE activity within normal range for healthy individuals, but the mean BChE value was lower compared to the control group; however, the difference was not statistically significant. On the other hand, patients with liver diseases (group 1) had serum BChE activity well below the reference interval for healthy subjects. The predominant hepatic source of serum BChE activity, the marked decreased synthesis with hepatocyte dysfunction, and its restoration with hepatocyte recovery suggested that serum BChE activity might be a more specific marker of liver dysfunction than the more traditional liver function tests [23].

5 AIDS

In patients with AIDS and abnormal D-xylose test, due to small intestinal dysfunction, BChE activity, total serum proteins, albumin, and cholesterol were significantly lower than in patients with a normal D-xylose absorptive test. Also, in this condition, BChE activity correlated with impairment of body composition and reflected protein-energy malnutrition [46].

6 HELLP syndrome

Pseudocholinesterase activity was reduced in pregnant women with HELLP syndrome and gradually increased with liver function recovery. There was a negative correlation between BChE activity and inflammatory response intensity, as measured by granulocyte count, ESR, body temperature, and IgA levels [47, 48].

7 Obesity and metabolic syndrome

BChE takes part in the protidosynthetic pathway and regulates the degradation of butyrylcholine, an intermediate of lipid metabolism, as demonstrated also by the close relation between serum BChE levels, cholesterol, and triacylglycerols [49].

BChE seems to be broadly involved in the pathophysiology of the metabolic syndrome. Its enzymatic activity is positively associated with cardiovascular risk factors: it is higher in patients who have hypertension, hyperlipidemia, and high body weight. On the other hand, it is inversely related to cardiovascular mortality: individuals with very low BChE activity have a higher mortality rate; BChE levels result low in patients who suffered acute myocardial infarction or underwent treatment with beta blockers [50, 51].

In experimental studies, during fattening in pigs, BChE activity significantly increased, probably due to an adaptive response of the hepatic synthesis of this enzyme to the increased lipid metabolism. Mice fed on a restricted diet had significantly lower serum BChE levels than mice fed a normal diet ad libitum; at the same time, an increase in BChE activity was observed in lean mice fed on a high carbohydrate diet. On the other hand, a marked reduction (40 %) in BChE activity occurred in the liver of genetically diabetic mice when starved for 24 h [6, 52, 53].

Liver BChE activity directly varied according to the protein content in the diet: high-protein diets produced the greatest increase in BChE activity in the liver compared to high-carbohydrate or high-fat diets [54].

BChE activity was significantly elevated in both type 1 and type 2 diabetes compared with the control subjects ($p < 0.001$); in these patients, serum BChE was correlated with serum fasting triacylglycerol concentration ($p < 0.001$) [55].

BChE may play a role in lipid metabolism, whether directly or through a synergistic action with cholesterol esterase. Several investigators have found significant relationships between cholinesterase activity and triacylglycerols, HDL cholesterol, and LDL cholesterol [6, 55–59].

One important issue arising from these findings is whether higher BChE activity is a cause or a consequence of dyslipidemia and metabolic syndrome. Several published reports on animal and human studies did not give a clear answer [60–64]. Interventions that primarily increase or

decrease blood lipids tend to have the same effect on BChE, but inhibition of BChE activity in vivo has been shown not to decrease lipid concentrations [61, 65–68]. BChE activity was reduced after treatment with bezafibrate but did not significantly change after treatment with statins [59].

In 1,097 healthy subjects, serum BChE activity was measured and metabolic syndrome risk factors assessed. Serum BChE activity correlated with fasting insulin levels (r=0.266, p< 0.001) and insulin resistance (HOMA-R) index (r=0.292, p< 0.001) and resulted higher in individuals with risk factors for metabolic syndrome. In two other studies on diabetic patients, BChE was found to be significantly correlated with serum insulin (r=0.622, p<0.001), C-peptide (r=0.652, p< 0.001), and free fatty acid (r=0.821, p< 0.001). Circumstantial evidence was provided demonstrating that insulin resistance and an increased flux of free fatty acids from adipose tissue to the liver stimulated the hepatic synthesis of serum BChE; these results suggest the involvement of PChE in the pathophysiology of the metabolic syndrome [49].

Also, the association with AST, ALT, and gamma-glutamyltransferase (GGT) activities, which are known to be associated with insulin resistance, probably reflects an association between BChE activity and the metabolic syndrome, of which fatty liver is a feature. Overweight patients with type 2 diabetes displayed significantly increased activities of serum ALT (172 % of mean values in controls), GGT (253 %), and BChE (139 %) and a strong correlation of BChE with serum triglycerides (r=0.760, p< 0.001) [5].

Increased BChE activity has been observed in nonobese as well as obese patients with fatty liver, whereas obese subjects without liver changes showed levels in the upper normal range. In subjects with fatty liver submitted to a low caloric diet, BChE activity decreased in parallel with the improvement of hepatic steatosis [69].

A striking parallel was also noted between plasma lecithin–cholesterol acyltransferase and serum BChE activity: both enzymes resulted to be lower than normal in liver disease and higher in endogenous hypertriglyceridemia and were also positively correlated with serum cholesterol and triglycerides, thus suggesting that both liver enzymes might be induced by an increased turnover of serum lipids and lipoproteins [70].

Blood pressure, as well, might be influenced causally by BChE because its substrate acetylcholine induces vasodilation by triggering nitric oxide release via endothelial muscarinic cholinergic receptors [71]. An excess of cholinesterase activity in the metabolic syndrome could also adversely affect endothelial function and ultimately increase blood pressure.

The gene for plasma cholinesterase is on chromosome 3; in addition to the known gene variants leading to low enzyme activity, a proportion of individuals show an additional cholinesterase electrophoresis band associated with an increased enzyme activity. This occurs with a frequency of 8 to 10 % among Europeans and is ascribed to the effects of another gene, cholinesterase (serum) 2 (*PChE2*), located on chromosome 5. It has been hypothesized that the region of chromosome 5 contains a gene for a protein that binds to BChE and increases its activity. Another explanation could be that high serum lipid concentrations may induce stereoscopic alteration in the enzymatic configuration that modifies BChE activity or altered expression of the enzyme-encoding gene that determines BChE concentration and activity [56].

8 Discussion

Serum concentrations and BChE activity seem to accurately reflect the availability of amino acidic substrates and/or a derangement in the protein synthesis due to hepatocellular damage; additionally, it seems adequate to distinguish liver and nonliver diseases. In cancer, with or without liver impairment, stress starvation stimulates an inflammatory cascade which blocks the synthesis of BChE, albumin, and other visceral proteins in favor of acute-phase protein synthesis. In these conditions, serum BChE results an accurate functional and prognostic indicator, useful for monitoring the clinical and therapeutic intervention according to the patient's survival expectance [72].

In the absence of inflammation, BChE could be also a valid index of nutritional support effectiveness. In patients with primary malnutrition, either in excess or in defect, BChE levels result strictly correlated with the classical indicators of the nutritional status such as albumin, lymphocyte count, cholesterol, and transferrin. Due to the large range of normality of serum BChE, this parameter is more suitable for repeated monitoring rather than single determination.

Clinical judgment certainly represents a fundamental hinge to combine with serum BChE evaluation as indicator of the severity of disease and/or protein-energy malnutrition the necessity of a nutritional support. Moreover, it is always preferable to associate BChE evaluation with other prognostic markers.

BChE activity assay seems to be a valid biological marker of malnutrition, inflammation, and liver synthetic ability with a relatively low cost and high clinical informative power [1]. Serum BChE determination is a routine clinical laboratory test, scheduled in all laboratory panels at hospital admission as well as for outpatient evaluation; on demand, it is also possible to add this test in the urgent exams' panels. Its cost is similar to that of other routine exams (serum glucose, urea, creatinine dosage, etc.), including the assay of albumin, prealbumin, transferrin, and lymphocyte count. BChE may therefore enter in a cluster of selected prognostic parameters, useful to complete the clinical judgment.

9 Conclusion

Serum BChE assessment should be included in routine clinical diagnostic procedures to evaluate patient clinical conditions, in particular in cases of inflammation and/or protein-energy malnutrition. This parameter has a prognostic value varying from disease to disease; for example, it indicates inadequate availability of substrates for liver synthesis and positively correlates with the effectiveness of nutritional support in case of malnutrition; BChE has a survival predictive role in cancer patients and seems to correlate with disease progression. Finally, reduced levels of BChE suggested negative outcomes (death or worsening of clinical conditions) in patients on artificial nutrition. Conversely to what happens in case of malnutrition, during metabolic syndrome (diabetes, hypertension, hyperlipidemia) and/or hepatic steatosis, BChE positively correlates with the presence of mild inflammation

In obesity, metabolic syndrome, lipid metabolism impairment, and fatty liver, BChE activity can also provide information on the patient's metabolism, habitual diet, and finally on the specific response to treatment.

Acknowledgments The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle* [73].

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