2-Hydroxybutyric Acid for Insulin Resistance

Subjects: Medicine, Research & Experimental | Endocrinology & Metabolism

Contributor: André Sousa

Diabetes mellitus type 2 (T2D), commonly known as non-insulin-dependent diabetes mellitus (NIDDM) is responsible for up to 95% of diabetic cases worldwide. It is defined as a chronic condition characterized by the loss and/or dysfunction of β-cells and insulin resistance (IR) in effector tissues, which is immediately recognized by an increase in glucose levels in the bloodstream, i.e., hyperglycemia.

Keywords: 2-hydroxybutyric acid ; impaired glucose tolerance ; insulin resistance ; type 2 diabetes mellitus

1. Introduction

The prevalence of T2D is increasing globally owing to population aging, the predominance of sedentary lifestyles in major western cultures and economic differences between developed and developing countries. According to the International Diabetes Federation's most recent reports, the number of undiagnosed people with diabetes has reached concerning levels, with 232 million people remaining undiagnosed for diabetes, indicating a dire need for new diagnosis methods and techniques that are both quick and inexpensive. The diabetic population is anticipated to reach 578 million people by 2030 and 700 million by 2045, with an increase in the death rate. Furthermore, 374 million people are at risk or extremely at risk of developing T2D, mostly in developed countries.

Only in the United States in 2019, at least USD 760 billion was spent on public health for diabetes prognosis and treatment. It becomes clear what future challenges governments and associations will face in order to change this reality and find answers to a growing problem and disease in the industrialized world [1].

Diabetes has already been associated with a high death rate; however it frequently leads to more serious comorbidities such as cardiovascular diseases (CVD), heart strokes, neuropathies, nephropathies, retinopathies, pulmonary diseases, depression, dementia, cancer, infectious diseases and, ultimately, to death [2][3].

2. Current Insights

In order to verify the potential of 2HB as an appropriate biomarker to detect early IR, a compilation of the outcomes is presented in **Table 1** that will be explored below.

Table 1. 2HB and related metabolites, pathologies and methodology of detection.

Study	Principal Metabolites Studied	Correlated Pathologic Conditions	Methodology	Outcomes
[4]	2HB	Insulin resistance (IR)	LC/MS and GC/MS	>levels of 2HB are related to diabetic and IGF patients
[5][6][7]			GC/MS	<2HB levels were observed after 6 months of gastric surgery. Furthermore, 2HB was used as inverse biomarker to predict improvement of pathology
[2]			HPLC and Oral Glucose Tolerance Testing (OGTT)	2HB can be used to predict hyperglycemia and β-cell dysfunction
[3]			LC/MS-MS and GC/MS	2HB showed in urine as a biomarker to T2D
[8]		IR and prostate cancer		2HB levels decreased after 3 months beginning treatment
[9]		IR and Impaired Glucose Tolerance (IGT)	UHPLC-MS/MS and GC/MS	2HB is an early marker for both IR and impaired glucose regulation
[10]			LC/MS-MS	Applied methodology was efficient to predict IR
[11]		IR and oxidative stress in low birthweight		Relation between low birthweight and IR
[12]		IR and dysregulations in thyroid hormone levels	UHPLC-MS/MS	2HB levels increased in IR, by metabolic overload and oxidative stress
[13]	2HB and α-tocopherol	IR and cardiovascular risk	UHPLC-MS and GC-MS	Increasing in 2HB and α-tocopherol levels were involved in IR and IGT
[14]	2HB and L-GPC	IR	n.m ***	High levels of 2HB and lower levels of L-GPC were associated with IR and IGT
[15]		IR and dysglicemia	HPLC-MS	
[16]	2HB and Branched-Chain Amino Acids (BCAA)	IR in youth	NMR and OGTT	BCAA and 2HB can predict IR in youth
[17]	Quantose M^Q mix *	IR and IGT	n.m ***	Improved insulin sensitivity and glucose tolerance, allowing to predict IR
[18]		IR and sclerosis multiple		Improved insulin sensitivity and glucose tolerance, allowing to predict IR
[19]		IR and non-alcoholic fatty liver disease and thrombocytopenia III	HPLC-MS and chemiluminescent microparticles immunoassay (for insulin specific)	Score was elevated in IR patients
[20]	Mix **	IR associated with atherosclerosis in coronary artery disease	n.m ***	A are a new set of biomarkers for IR and endothelial dysfunction in T2D patients
Summary	2HB	Mainly IR	High throughput technologies (not routine methods)	Higher levels of 2HB is positively associated with IR

* α-hydroxybutyrate, oleate, insulin and L-linoleoyl-glycerophosphocholine (L-GPC). ** Mix—α-hydroxybutyrate, YKL-40, leptin, CD36, IL-18, RBP4, resistin, chemerin. *** n.m—not mentioned.

2.1. 2HB

Ref. [9] has looked through the main biofunction of 2HB and his results pointed that this biomolecule is synthesized in response to the oxidative stress and lipid peroxidation caused by IR and IGT regulation; in this way, it is considered as an

early marker to both conditions. This author has also settled a 2HB concentration cut-off of 5 µg/mL, with values above indicating the presence of IR and IGT. Furthermore, [4], in his study, demonstrated that high levels of 2HB are common in T2D, also suggesting that it can be caused by the IR. Furthermore, Varvel, S. (2015) showed that measuring serum 2HB is a reliable method to screen hyperglycemia and β-cell dysfunction, giving fast results without using many resources. Salgado-Bustamante, Ref. [11] reported that an increase of 2HB was reported in the urine of T2D patients.

Looking specifically at IR and 2HB, Ref. [12] has demonstrated that 2HB levels increased in IR, potentially due to metabolic overload (through BCAA and free fatty acids) and oxidative stress (by the higher intracellular $NADH/NAD^+$ ratio). In addition, the author showed that the pharmacological approach against IR resulted in a decrease in 2HB levels, which is consistent with the results presented until now.

The mechanism adjacent to IGT was also explored in order to better understand the biopathology underlies IR. For that, Ref. [7] investigated the infection with *S. aureus* and reported that the bacteria produce an insulin-binding protein that reduces glucose uptake by blocking insulin receptors, resulting in metabolic syndrome. However, an antibody fully capable of disabling the blocker protein was developed, and 2HB was used to grant the effectiveness of the treatment. Results showed that levels of 2HB reduced among time of the study.

Ref. [11] verified the relation between low birthweight and IR, attending to 2HB levels. Even though results were only expressed in women, they showed that biochemical pathways modified on adulthood were a consequence of weight at birth, which are connected directly with IR.

In a different study, Ref. [6] investigated the effect of a gastric bypass surgery in the IR. He verifies that 2HB levels have decreased 6 months following surgery, when compared to the levels at the moment of the gastric procedure, which was an indicator of improvement of IR. The author suggested that this mechanism is due to a precursor of 2KB—2-ketobutyric acid—that is increased in oxidative stress conditions related to glutathione synthesis. When overexpressed, this metabolic pathway produces 2HB as a byproduct, which can be used to detect IR, e.g., being an early biomarker in the non-diabetic population [5].

In a study involving anticancer therapy for prostate cancer, Ref. [8] (2012) explored the effect of therapy on gonadal androgen therapy in IR. The results showed that 2HB levels decreased after 3 months of treatment.

Thus, the authors showed that higher levels of 2HB are an indicator of IR. It is important to refer to the fact that age, gender and body mass index do not interfere with any result.

2.2. Relationship between 2HB and Other Metabolites

Ref. [13] has defined the 2HB concentration in normal conditions as 1.60 ± 0.57 µg/mL. It was also described that α-tocopherol is dependent on 2HB to be synthesized. This way, an increase in 2HB leads to an increase in and α-tocopherol levels, which will on the one hand induce IR and IGT, and on the other hand increase other risk factors to T2D and/or hypertension development. Ref. [15] reported that high levels of 2HB and lower levels of L-GPC were associated with IR and IGT. These two markers were also used to control the progression of IR among 3 years, demonstrating that they are a good method to predict IR. During patients' follow up, a reduction from 4.21 ± 2.01 to 3.83 ± 1.73 µg/mL in 2HB concentration and an increase from 15.41 ± 6.60 to 16.24 ± 7.03 µg/mL in L-GPC concentration. The author also showed that there is an inverse relationship between β-cell dysfunction and 2HB. All those factors lead to an increased risk of developing T2D. Ref. [6] has also reported that the increase of 2HB leads to a consequent reduction of L-GPC when IR is under treatment. Other study conducted by [16] showed the relationship between 2HB and Branched-Chain Amino Acids (BCAA), where the 2HB participates in substrate BCAA synthesis. They demonstrated that fasting concentrations of BCAA and 2HB can predict IR in youth, which can prevent risks of developing other diseases in adulthood. Furthermore, the author reported that these two markers can predict incipient deterioration of β-cell function and IGT. In a new study, Ref. [20] has reported that the use of 2HB as a biomarker accurately differentiates sensitive patients from those resistant to insulin. Along with 2HB, other molecules were described to improve the diagnosis. It was reported the enhanced YKL-40 and soluble CD36 released by IGF-1 activation, which lead to high levels of oxidative stress. Il-18 and resistin were also demarked to become overexpressed in IR, in this way potentiating the previously described oxidative stress. Finally, RBP4 and chemerin were reported with 2HB, once these molecules are related to the insensitivity of GLUT-4, an important glucose transporter in muscle cells. Thus, these biomolecules panels were considered to be good biomarkers for IR and endothelial dysfunction in T2D patients. Specifically, 2HB was directly related to the influence of β-cell action on insulin levels, increasing glutathione production.

2.3. Quantose M^Q

The Quantose M^Q score is the result of the measure of insulin, 2HB, linoleoyl-glycerophosphocholine, and oleate. This score allows detecting patients with IR in earlier stages.

Some studies done by [18] demonstrated that Quantose M^Q was an efficient diagnostic biomolecular panel to IR, with 51% of the population being detected accurately. It also has been shown to reduce the Quantose score when insulin sensitivity and glucose tolerance are improved. Ref. [17] reported that the use of an antidiabetic medicine (pioglitazone) reduced the concentration of 2HB by 6% and of insulin by 2%. The author also wrote that it “may serve as a useful clinical test to identify and monitor therapy in insulin-resistant patients”, and is a possible marker for monitoring therapeutic intervention.

Furthermore, Ref. [19] showed that the mean Quantose M^Q score was elevated in IR patients. The author explored the reason for that increasing in the score, pointing to non-alcoholic fatty liver disease as a possible cause, which involves NAFLD (involved in oxidative stress, including a set of molecules such as adipokines, chemokine and pro-inflammatory cytokines). It was also described that the presence of other diseases and the condition of IR lead to the increase in Quantose score.

It is important to point again that IR was not related to sex, age, weight, and body mass index.

References

1. International Diabetes Federation Atlas. 463 People Living with Diabetes Million; The International Diabetes Federation: Brussels, Belgium, 2019; ISBN 9782930229874.
2. Varvel, S.A.; Pottala, J.V.; Thiselton, D.L.; Caffrey, R.; Dall, T.; Sasinowski, M.; McConnell, J.P.; Warnick, G.R.; Voros, S.; Graham, T.E. Serum α-hydroxybutyrate (α-HB) predicts elevated 1 h glucose levels and early-phase β-cell dysfunction during OGTT. BMJ Open Diabetes Res. Care 2014, 2, e000038.
3. Salgado-Bustamante, M.; Rocha-Viggiano, A.K.; Rivas-Santiago, C.; Magaña-Aquino, M.; López, J.A.; López-Hernández, Y. Metabolomics applied to the discovery of tuberculosis and diabetes mellitus biomarkers. Biomark. Med. 2018, 12, 1001–1013.
4. Xu, F.; Tavintharan, S.; Sum, C.F.; Woon, K.; Lim, S.C.; Ong, C.N. Metabolic signature shift in type 2 diabetes mellitus revealed by mass spectrometry-based metabolomics. J. Clin. Endocrinol. Metab. 2013, 98, E1060–E1065.
5. Lin, Z.; Gonçalves, C.M.V.; Dai, L.; Lu, H.-M.; Huang, J.-H.; Ji, H.; Wang, D.-S.; Yi, L.-Z.; Liang, Y.-Z. Exploring metabolic syndrome serum profiling based on gas chromatography mass spectrometry and random forest models. Anal. Chim. Acta 2014, 827, 22–27.
6. Shantavasinkul, P.C.; Muehlbauer, M.J.; Bain, J.R.; Ilkayeva, O.R.; Craig, D.M.; Newgard, C.B.; Svetkey, L.P.; Shah, S.H.; Torquati, A. Improvement in insulin resistance after gastric bypass surgery is correlated with a decline in plasma 2-hydroxybutyric acid. Surg. Obes. Relat. Dis. 2018, 14, 1126–1132.
7. Liu, Y.; Liu, F.-J.; Guan, Z.-C.; Dong, F.-T.; Cheng, J.-H.; Gao, Y.-P.; Li, D.; Yan, J.; Liu, C.-H.; Han, D.-P.; et al. The extracellular domain of Staphylococcus aureus LtaS binds insulin and induces insulin resistance during infection. Nat. Microbiol. 2018, 3, 622–631.
8. Saylor, P.J.; Karoly, E.D.; Smith, M.R. Prospective Study of Changes in the Metabolomic Profiles of Men during Their First Three Months of Androgen Deprivation Therapy for Prostate Cancer. Am. Assoc. Cancer Res. 2012, 18, 13.
9. Gall, W.E.; Beebe, K.; Lawton, K.A.; Adam, K.P.; Mitchell, M.W.; Nakhle, P.J.; Ryals, J.A.; Milburn, M.V.; Nannipieri, M.; Camastra, S.; et al. α-Hydroxybutyrate Is an Early Biomarker of Insulin Resistance and Glucose Intolerance in a Nondiabetic Population. PLoS ONE 2010, 5, e10883.
10. Zhang, Q.; Ford, L.A.; Goodman, K.A.; Freed, T.A.; Hauser, D.M.; Conner, J.K.; Vroom, K.E.T.; Toal, D.R. LC–MS/MS method for quantitation of seven biomarkers in human plasma for the assessment of insulin resistance and impaired glucose tolerance. J. Chromatogr. B 2016, 1038, 101–108.
11. Metrustry, S.J.; Karhunen, V.; Edwards, M.H.; Menni, C.; Geisendorfer, T.; Huber, A.; Reichel, C.; Dennison, E.M.; Cooper, C.; Spector, T.; et al. Metabolomic signatures of low birthweight: Pathways to insulin resistance and oxidative stress. PLoS ONE 2018, 13, e0194316.
12. Ferrannini, E.; Iervasi, G.; Cobb, J.; Ndreu, R.; Nannipieri, M. Insulin resistance and normal thyroid hormone levels: Prospective study and metabolomic analysis. Am. J. Physiol.-Endocrinol. Metab. 2017, 312, 429–436.
13. Peddinti, G.; Cobb, J.; Yengo, L.; Froguel, P.; Kravić, J.; Balkau, B.; Tuomi, T.; Aittokallio, T.; Groop, L. Early metabolic markers identify potential targets for the prevention of type 2 diabetes. Diabetologia 2017, 60, 1740–1750.

14. Lowe, W.L.; Bain, J.R. “Prediction is very hard, especially about the future”: New biomarkers for type 2 diabetes? Diabetes 2013, 62, 1384–1385.
15. Ferrannini, E.; Natali, A.; Camastra, S.; Nannipieri, M.; Mari, A.; Adam, K.P.; Milburn, M.V.; Kastenmüller, G.; Adamski, J.; Tuomi, T.; et al. Early metabolic markers of the development of dysglycemia and type 2 diabetes and their physiological significance. Diabetes 2013, 62, 1730–1737.
16. Tricò, D.; Prinsen, H.; Giannini, C.; de Graaf, R.; Juchem, C.; Li, F.; Caprio, S.; Santoro, N.; Herzog, R. Elevated α-Hydroxybutyrate and Branched-Chain Amino Acid Levels Predict Deterioration of Glycemic Control in Adolescents. J. Clin. Endocrinol. Metab. 2017, 102, 2473–2481.
17. Tripathy, D.; Cobb, J.E.; Gall, W.; Adam, K.P.; George, T.; Schwenke, D.C.; Banerji, M.A.; Bray, G.A.; Buchanan, T.A.; Clement, S.C.; et al. A novel insulin resistance index to monitor changes in insulin sensitivity and glucose tolerance: The ACT NOW study. J. Clin. Endocrinol. Metab. 2015, 100, 1855–1862.
18. Ruiz-Argüelles, A.; Méndez-Huerta, M.A.; Lozan, C.D.; Ruiz-Argüelles, G.J. Metabolomic profile of insulin resistance in patients with multiple sclerosis is associated to the severity of the disease. Mult. Scler. Relat. Disord. 2018, 25, 316–321.
19. López-Trujillo, M.A.; Olivares-Gazca, J.M.; Cantero-Fortiz, Y.; García-Navarrete, Y.I.; Cruz-Mora, A.; Olivares-Gazca, J.C.; Murrieta-Álvarez, I.; León-Peña, A.A.; Ruiz-Delgado, G.J.; Ruiz-Argüelles, G.J. Nonalcoholic Fatty Liver Disease and Thrombocytopenia III: Its Association With Insulin Resistance. Clin. Appl. Thromb. 2019, 25, 4–7.
20. Ikmal, S.I.Q.S.; Huri, H.Z.; Vethakkan, S.R.; Ahmad, W.A.W. Potential biomarkers of insulin resistance and atherosclerosis in type 2 diabetes mellitus patients with coronary artery disease. Int. J. Endocrinol. 2013, 2013, 698567.