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COMMENTARY

Unraveling the Sulfur Insulin Deformation Hypothesis: A Novel Therapeutic Avenue for Type 2 Diabetes

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Abstract

This manuscript presents the “Sulfur Insulin Deformation Hypothesis,” proposing that organic sulfur deficiency contributes to the improper formation of insulin’s disulfide bonds, leading to insulin structural deformation and functional impairment in Type 2 Diabetes (T2D). The hypothesis suggests that rather than insulin resistance being the primary defect, T2D may originate from sulfur-mediated misfolding of insulin, resulting in reduced receptor binding and hyperglycemia. The authors explore the role of Methylsulfonylmethane (MSM), an organosulfur compound, as a potential therapeutic by restoring sulfur availability, enhancing disulfide bond formation, and improving insulin stability. A case report is included, highlighting successful glycemic control after MSM supplementation in a patient with diabetes. While the initial findings support the hypothesis, further clinical studies are essential to validate MSM’s efficacy as a novel treatment for T2D.

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Human insulin is a peptide hormone essential for regulating glucose homeostasis. It is synthesized as preproinsulin in the beta cells of the pancreas and directed into the endoplasmic reticulum, where it is cleaved to form proinsulin. Proinsulin consists of the A chain, B chain, and C-peptide. In the endoplasmic reticulum, proinsulin folds into its active conformation, stabilized by crucial disulfide bonds. These bonds hold the structure together, with two inter-chain disulfide bonds linking the A and B chains, and one intra-chain bond within the A chain, essential for stability. Afterward, proinsulin is processed in secretory granules, where the C-peptide is removed, forming mature insulin, which is stored until secretion in response to elevated blood glucose[1].

Insulin, a polypeptide of 51 amino acids, consists of an A chain (21 amino acids) and a B chain (30 amino acids) linked by two inter-chain disulfide bridges, with an additional intra-chain bond in the A chain. These disulfide bonds are critical for maintaining insulin's three-dimensional structure, which is essential for binding to the insulin receptor. Proper folding and bond formation ensure that the receptor-binding domains are correctly presented for biological activity[2].

Organic sulfur plays a pivotal role in the stabilization of various biological compounds, hormones, and enzymes by regulating and forming sulfide bonds, particularly disulfide bonds, which are crucial for maintaining the structural and functional integrity of proteins. Sulfur is found in several amino acids, such as cysteine and methionine, which contribute significantly to the conformation and stability of biomolecules[3]. Cysteine, in particular, is essential for the formation of disulfide bonds, as its thiol (-SH) group allows for the creation of covalent links between polypeptide chains or within the same chain, thereby stabilizing the three-dimensional structure of proteins[4].

In hormones such as insulin, disulfide bonds are fundamental to maintaining a specific conformation that is required for receptor binding and subsequent biological activity. Without these covalent sulfur linkages, the hormone would lose its structural stability, leading to impaired signaling and metabolic dysregulation[2]. Similarly, in enzymes, disulfide bonds contribute to the correct folding and assembly of catalytic domains, ensuring that the active sites are appropriately formed and accessible for substrate binding. This contributes not only to enzymatic efficiency but also to resistance against denaturation in varying physiological conditions[5].

Sulfur also has a crucial role in the antioxidant systems of the body, particularly through glutathione, a tripeptide containing cysteine.

Glutathione contains a sulfhydryl group that allows it to undergo oxidation-reduction reactions, which help to maintain the redox state of cells and protect them from oxidative stress. The dynamic formation and reduction of disulfide bonds in glutathione are vital for detoxifying reactive oxygen species (ROS) and maintaining protein stability under oxidative conditions[6].

Moreover, sulfur bridges contribute to the stability of extracellular proteins and are particularly significant in structural proteins like keratin, found in hair, nails, and skin, where they confer rigidity and strength[7]. The versatility of sulfur bonds in stabilizing diverse biomolecules underscores their importance in maintaining the structural and functional homeostasis of the body. Proper regulation of sulfur-containing compounds and their bonding mechanisms is, therefore, essential for preserving the activity of hormones, enzymes, and structural proteins, ultimately ensuring normal physiological function[8].

Biochemically, the integrity and functionality of the insulin molecule rely heavily on the presence of correctly formed disulfide bonds, which are established between specific cysteine residues. Human insulin comprises two peptide chains, designated as A and B chains, which are linked by two inter-chain disulfide bonds, with an additional intra-chain disulfide bond within the A chain. These bonds are crucial for maintaining the active conformation of insulin, which is necessary for its interaction with the insulin receptor (IR) on the target cells. Any disruption in these disulfide bonds can significantly alter the tertiary structure of insulin, impairing its biological activity[9].

In this proposed hypothesis, a deficiency in organic sulfur can be implicated in the improper formation or stability of these disulfide bonds, ultimately leading to insulin deformation. Organic sulfur is critical for synthesizing sulfur-containing amino acids like cysteine, which is a precursor for the formation of disulfide bonds. In the absence of adequate sulfur, the thiol (-SH) groups of cysteine residues may not undergo appropriate oxidation to form disulfide linkages (-S-S-), resulting in an improperly folded insulin protein[10]. Such misfolding not only reduces the affinity of insulin for its receptor but also makes

it more susceptible to degradation, thus reducing the effective concentration of functional insulin in the circulation.

Mechanistically, when insulin with deformed disulfide bonds attempts to bind to the insulin receptor, the receptor's tyrosine kinase domain is not properly activated, leading to suboptimal autophosphorylation. This lack of efficient receptor activation disrupts the downstream signaling cascade, notably affecting the phosphorylation of insulin receptor substrates (IRS). Consequently, the activation of the phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) pathway, which is vital for glucose transporter type 4 (GLUT4) translocation to the cell membrane, is impaired. This results in decreased glucose uptake by muscle and adipose tissues, leading to hyperglycemia, one of the defining characteristics of T2D[11].

Furthermore, the hypothesis proposes that, instead of insulin resistance originating from defects within the target cells, the issue lies in the bioavailability and structural stability of insulin itself. Insulin, lacking proper disulfide bonds due to sulfur deficiency, may also fail to inhibit hepatic glucose production effectively, further contributing to elevated blood glucose levels. Thus, targeting sulfur metabolism and ensuring sufficient organic sulfur intake may improve the structural stability of insulin, restore its biological activity, and potentially reverse the hyperglycemic condition associated with T2D.

Methylsulfonylmethane (MSM) is an organic sulfur compound that has potential therapeutic applications in Type 2 Diabetes (T2D) in line with the "Sulfur Insulin Deformation Hypothesis." According to this hypothesis, T2D results not merely from insulin resistance but from the deformation of insulin molecules, particularly involving defects in the disulfide bonds due to a deficiency of organic sulfur. MSM, as a rich source of bioavailable sulfur, could play a crucial role in addressing this underlying issue by providing the sulfur necessary for proper disulfide bond formation in insulin[12].

MSM can contribute to restoring the integrity of insulin through several biochemical mechanisms. Upon ingestion, MSM is absorbed and metabolized, releasing sulfur that can be used for the synthesis of sulfur-containing amino acids, such as cysteine. Cysteine residues in insulin are responsible for the formation of disulfide bonds, which are vital for maintaining the correct tertiary and quaternary structure of the insulin molecule. In the context of T2D, where insufficient organic sulfur leads to improper insulin folding and deformation, supplementation with MSM could provide the sulfur required to correct these deficiencies[13].

Mechanistically, when MSM is metabolized and incorporated into cellular sulfur pools, it facilitates the proper formation of disulfide bonds between cysteine residues in proinsulin during its folding process in the endoplasmic reticulum. This correct disulfide bond formation is essential to create a structurally stable and biologically active form of insulin, which has a high binding affinity for the insulin receptor (IR). As a result, properly formed insulin molecules can effectively bind to the receptor on the target cells, leading to optimal activation of the receptor’s intrinsic tyrosine kinase activity[14].

This receptor activation triggers a cascade of intracellular signaling events, beginning with the phosphorylation of insulin receptor substrates (IRS). Activated IRS then stimulates the phosphoinositide 3-kinase (PI3K) pathway, leading to the activation of protein kinase B (Akt). Akt plays a crucial role in the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, allowing increased glucose uptake by muscle and adipose tissues. The increased glucose uptake results in lower blood glucose levels, effectively mitigating hyperglycemia[15].

Additionally, MSM might help reduce oxidative stress, which is often elevated in individuals with T2D and can further

damage insulin structure and function. By acting as an antioxidant, MSM can help maintain the redox balance within beta cells and other insulin-producing or -responding tissues, thus ensuring that cysteine residues remain available for disulfide bond formation rather than being oxidized by reactive oxygen species (ROS)[16][17].

Thus, MSM, by providing a bioavailable form of sulfur, can directly address the sulfur deficiency posited in the "Sulfur Insulin Deformation Hypothesis," leading to the restoration of insulin's structural integrity and functionality. This makes MSM a promising therapeutic candidate, potentially able to tackle the root cause of T2D as proposed by this hypothesis, rather than merely treating its symptoms or attempting to bypass insulin resistance[13].

A promising result has emerged from the case report of a 22-year-old patient diagnosed with MODY (Maturity Onset Diabetes of the Young), who exhibited classic symptoms such as frequent nocturnal urination. His initial HbA1c (Glycated Hemoglobin) was recorded at 8% (normal range: 4%-5.6%), indicating poor long-term glucose control. Additionally, the patient had a high level of insulin resistance, with fasting blood glucose levels of approximately 220 mg/dL (normal range: 70-100 mg/dL) and postprandial glucose levels around 360 mg/dL (normal range: <140 mg/dL).

The patient was started on an exercise regimen along with Methylsulfonylmethane (MSM) supplementation at a dose of 1000 mg twice daily for three months. After this period, all glucose levels improved significantly, with fasting glucose dropping to 90 mg/dL, postprandial glucose at 130 mg/dL, and HbA1c reducing to 5.4%, all within normal ranges.

This initial success supports the "Sulfur Insulin Deformation Hypothesis" and highlights the potential of MSM as a therapeutic approach to restore insulin functionality by enhancing disulfide bond formation. However, further clinical trials are urgently needed to confirm these findings and explore MSM's broader efficacy in managing diabetes.

Conclusion: This research presents a novel hypothesis for the pathogenesis of Type 2 Diabetes (T2D), suggesting that structural deformation of insulin, resulting from a deficiency in organic sulfur, may be a more plausible explanation for the disease compared to the conventional concept of insulin resistance. This hypothesis emphasizes the critical role of organic sulfur in maintaining proper disulfide bond formation within the insulin molecule. The study proposes that supplementation with Methylsulfonylmethane (MSM) could play a significant therapeutic role in T2D by restoring the correct structural conformation of insulin and enhancing its biological functionality. By addressing the underlying sulfur deficiency, this approach offers a new perspective for therapeutic intervention, aiming to target the root cause of T2D rather than simply managing its symptoms.

Statements and Declarations

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Conflict of Interests

The authors declare that there are no conflicts of interest.

Informed consent

Before taking this case, information was given to the patient, and informed consent was obtained for follow-up and consent to share the investigations, figures, and any required data.

Ethical statement

This case was conducted in accordance with the Declaration of Helsinki and meets the CARE guidelines criteria. Informed consent was obtained from the patient for follow-up, including permission for the publication of all photographs, lab results, and images included herein.

References

1. ^*Fu Z, Gilbert ER, Liu D (2013). "Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes". Current diabetes reviews. 9(1): 25–53.*
2. a, b*Vinther TN, Norrman M, Ribel U, Huus K, Schlein M, Steensgaard DB, Pedersen TÅ, Pettersson I, Ludvigsen S, Kjeldsen T, Jensen KJ, Hubálek F (2013). "Insulin analog with additional disulfide bond has increased stability and preserved activity". Protein science: a publication of the Protein Society. 22(3): 296–305. doi:10.1002/pro.2211.*
3. ^*Francioso A, Baseggio Conrado A, Mosca L, Fontana M (2020). "Chemistry and Biochemistry of Sulfur Natural Compounds: Key Intermediates of Metabolism and Redox Biology". Oxidative medicine and cellular longevity. 2020: 8294158. doi:10.1155/2020/8294158.*
4. ^*Robinson PJ, Bulleid NJ (2020). "Mechanisms of Disulfide Bond Formation in Nascent Polypeptides Entering the Secretory Pathway". Cells. 9(9): 1994. doi:10.3390/cells9091994.*
5. ^*Fu J, Gao J, Liang Z, Yang D (2020). "PDI-Regulated Disulfide Bond Formation in Protein Folding and Biomolecular Assembly". Molecules (Basel, Switzerland). 26(1): 171. doi:10.3390/molecules26010171.*
6. ^*Mukwevho E, Ferreira Z, Ayeleso A (2014). "Potential role of sulfur-containing antioxidant systems in highly oxidative environments". Molecules (Basel, Switzerland). 19(12): 19376–19389. doi:10.3390/molecules191219376.*
7. ^*Bragulla HH, Homberger DG (2009). "Structure and functions of keratin proteins in simple, stratified, keratinized and cornified epithelia". Journal of anatomy. 214(4): 516–559. doi:10.1111/j.1469-7580.2009.01066.x.*
8. ^*Künstler A, Gullner G, Ádám AL, Kolozsváriné Nagy J, Király L (2020). "The Versatile Roles of Sulfur-Containing Biomolecules in Plant Defense-A Road to Disease Resistance". Plants (Basel, Switzerland). 9(12): 1705. doi:10.3390/plants9121705.*
9. ^*Liu M, Weiss MA, Arunagiri A, Yong J, Rege N, Sun J, Haataja L, Kaufman RJ, Arvan P (2018). "Biosynthesis, structure, and folding of the insulin precursor protein". Diabetes, obesity & metabolism. 20 Suppl 2(Suppl 2): 28–50. doi:10.1111/dom.13378.*

10. ^*Ulrich K, Jakob U (2019). "The role of thiols in antioxidant systems". Free radical biology & medicine. 140: 14–27. doi:10.1016/j.freeradbiomed.2019.05.035.*
11. ^*Choi E, Bai XC (2023). "The Activation Mechanism of the Insulin Receptor: A Structural Perspective". Annual review of biochemistry. 92: 247–272. doi:10.1146/annurev-biochem-052521-033250.*
12. ^*Sousa-Lima I, Park SY, Chung M, Jung HJ, Kang MC, Gaspar JM, Seo JA, Macedo MP, Park KS, Mantzoros C, Lee SH, Kim YB (2016). "Methylsulfonylmethane (MSM), an organosulfur compound, is effective against obesity-induced metabolic disorders in mice". Metabolism: clinical and experimental. 65(10): 1508–1521. doi:10.1016/j.metabol.2016.07.007.*
13. a, b*Wong T, Bloomer RJ, Benjamin RL, Buddington RK (2017). "Small Intestinal Absorption of Methylsulfonylmethane (MSM) and Accumulation of the Sulfur Moiety in Selected Tissues of Mice". Nutrients. 10(1): 19. doi:10.3390/nu10010019.*
14. ^*Bulleid NJ (2012). "Disulfide bond formation in the mammalian endoplasmic reticulum". Cold Spring Harbor perspectives in biology. 4(11): a013219. doi:10.1101/cshperspect.a013219.*
15. ^*Boucher J, Kleinridders A, Kahn CR (2014). "Insulin receptor signaling in normal and insulin-resistant states". Cold Spring Harbor perspectives in biology. 6(1): a009191. doi:10.1101/cshperspect.a009191.*
16. ^*Caturano A, D'Angelo M, Mormone A, Russo V, Mollica MP, Salvatore T, Galiero R, Rinaldi L, Vetrano E, Marfella R, Monda M, Giordano A, Sasso FC (2023). "Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications". Current issues in molecular biology. 45(8): 6651–6666. doi:10.3390/cimb45080420.*
17. ^*Butawan M, Benjamin RL, Bloomer RJ (2017). "Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement". Nutrients. 9(3): 290. doi:10.3390/nu9030290.*