MedCrave Step into the World of Research
International Journal of Complementary & Alternative Medicine

Review Article

Open Access CrossMark

Can biophotonic therapy ameliorate the metabolic sequelae of NIDDM?

Abstract

Since antiquity, humans have sought the healing powers of sunshine to resolve many illnesses and restore a sensation of health and wellness. In recent publications, it has been reported that biophotonic treatment resulted in improvements in hemoglobin A1c and SpO2 concentrations in human subjects. In an animal study in which biophotonic treatment was applied to skeletal muscle in two models of Type 2 diabetes (NIDDM/T2DM), biophotonic treatment resulted in normalization of fasting and response plasma glucose concentrations and in an improvement in glycogen synthesis in skeletal muscle, likely secondary at least in part to improved GLUT4 actions and insulin sensitivity resulting in improved peripheral glucose uptake and oxidation and by increases in ATP generation in skeletal muscle. Because the biochemical mechanisms of carbohydrate metabolism and their contributions to the development of NIDDM are similar in both humans and in the animal models studied, the question arises as to whether biophotonic therapy might undergo consideration as an adjunct in the treatment of hyperglycemia, elevated HbA1c, peripheral oxygen delivery and wound healing in clinical management of NIDDM/T2DM. Biophotonic therapies have been widely used in the treatment of various infectious diseases and as an adjunct in anti-aging medicine, but the observations on parameters of intermediary metabolism in humans and animal models of NIDDM/T2DM reflect new findings believed to be of significant importance if applied to the clinical management of obesity, NIDDM and impaired glycemic states in humans.

Keywords: obesity, Type 2 diabetes, NIDDM, glycemia, HbA1c, pO2

Volume 17 Issue 2 - 2024

Orien L Tulp, PhD, MD, FACN, CNS,[1,2]
George P Einstein, PhD, DSc[1,2]

[1]Professor, Colleges of Medicine and Graduate Studies, University of Science Arts and Technology, Montserrat, British West Indies
[2]The Einstein Medical Institute, North Palm Beach, FL USA

Correspondence: Orien L Tulp, PhD, MD, FACN, CNS, Professor, Colleges of Medicine and Graduate Studies, University of Science Arts and Technology, Montserrat, British West Indies MSR1110, Email o.tulp@usat.edu

Received: April 01, 2024 | **Published:** April 19, 2024

Introduction

The application of biophotonics therapy has often been cited as an effective adjunct in the treatment of infectious diseases of viral and microbial origin for much of the past century.[1–3] More recently, Tulp et al and Miley demonstrated that biopotonics exposure in human subjects resulted in an apparent photodissociation of oxygen from oxyhemoglobin within 2 hours of UV exposure, thereby improving blood pO2 delivery to peripheral tissues.[4,5] In the recent studies cited, a significant decrease in HbA1c was noted 120 minutes after biphotonic treatment was completed in the human subjects. The clinical improvements in SpO2 persisted for up to 30 days post-biphotonic treatment in Miley's studies. In studies in the diabetic *db/db* mouse model of obesity and NIDDM, improvements in carbohydrate metabolism, glycogen synthesis, and in ATP synthesis in skeletal muscle were observed following biophotonic exposure.[6] Thus, these results when considered together, generate speculation that controlled low dosage biophotonic exposure to selected wavelengths of UV light could be an effective adjunct in wound healing processes and in the clinical management of NIDDM/T2DM. Peripheral oxygen delivery and availability is an important contributor to wound healing and other physiologic and metabolic processes and may become decreased in magnitude as HbA1c levels increase also with progressive derangements in blood glucose control in NIDDM/T2DM, and the glycemic derangements may become reversible following timely photon excitation.[7–9]

The contributions of glucocorticoid actions on insulin-stimulated formation and intracellular cytoplasmic translocation of GLUT4 transporters from the endoplasmic reticulum to the plasma membrane has been well documented.[10–19] When the regulation of the transporters become disrupted due to glucocorticoids or other factors, the typical physiologic response is contributory to an increase in insulin secretion in an apparent physiologic attempt to overcome the impediment in glucose transporter actions to support efficient glucose oxidation.[15] The metabolic cascade of events which likely follow contributes to the progressive development of insulin resistance along with its pathophysiologic sequelae in cells and tissues. Thus, the pathophysiologic influences on skeletal muscle, adipose tissue depots and other tissues may further exaggerate the impact of hyper insulinemia and insulin resistance. These adverse pathophysiologic influences may extend to additional tissues including skeletal muscle, brain and others that are also dependent on molecular glucose for oxidative metabolism.[12,15,19] Therefore, pharmacologic or physiologic measures that improve the efficacy and activity of GLUT4 transporters, in addition to the effects of cellular 2,3 DPG and oxygen delivery to peripheral tissues would seem to be an effective strategy to restore GLUT4 transporter functions, permit the restoration of endoplasmic reticulum synthesis and intracellular translocation to the plasma membranes, improve cellular glucose uptake and oxidation, and thus diminish the overall magnitude of insulin resistance in the various tissues of the obese phenotype of this and other genetically obese rat strains and in humans with NIDDM.[5]Insulin is known to impact multiple aspects of energy metabolism and storage, including lipogenesis, activation of pre-adipocytes, and substrate oxidative processes, all of which may serve as primary or secondary factors that can contribute to caloric efficiency, excess energy storage in adipose tissue depots and metabolic events in other tissues, including hepatic fatty acid and glycogen synthesis and storage.[6,7,10–21.]

In several studies, *db/db* mice from the Charles River laboratories were used to model phase 1 to phase 3 of type II diabetes and obesity.[6] Mice that are homozygous for the diabetes spontaneous mutation (*Lepr^{db}*) demonstrate morbid obesity, chronic hyperglycemia, progressive deterioration, andpancreatic beta cell atrophy and become hypoinsulinemic. Affected *db/db* mice are polyphagic, polydipsic, and

Submit Manuscript | http://medcraveonline.com

©2024 Tulp et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Copyright: ©2024 Tulp et al.

polyuric throughout most or all of their adolescence and adulthood.[6] The authors reported that the onset of obesity began at three to four weeks of age in this as in other animal strains where NIDDM develops.[9,20] The BKS background in *db/db* mice brings about an uncontrolled rise in blood glucose concentrations, severe depletion of insulin-producing beta-cells of the pancreatic islets, peripheral neuropathy, myocardial disease and early death typically by ten months of age.[6] Exogenous insulin deficiency results in progressive loss of control of blood glucose levels, while gluconeogenic enzyme activity increased. Metabolic efficiency and fat accretion may become increased during early life and adolescence in obese-NIDDM models, while wound healing processes became delayed.[6,20–22] In other studies, adrenal ablation resulted in improvements in glycemic and thermogenic parameters, implicating a contributory counter regulatory role of glucocorticoid hormones and insulin sensitivity in the progression of insulin resistance and in the metabolic derangements and expression of nonshivering thermogenesis.[10,19,23] Glucocorticoid hormones impair the biosynthesis and intracellular translocation of GLUT4 glucose transporters in muscle and adipose tissues, thereby contributing to a deterioration in the insulin-dependent process of glucose uptake and in diminished insulin sensitivity, resulting in hyperglycemia and increases in hemoglobin glycation that are proportional to the magnitude of hyperglycemia.[12,15–17] Because the glycated hemoglobin process is a glucose dependent, non-enzymatic process, the resulting glycation persists proportional to mean glucose concentrations throughout the remaining lifespan of the erythrocytes. Hemoglobin glycation impacts on 2,3 DPG actions and results in less efficient transport and release of oxygen in peripheral tissues, thereby contributing to the impairments in the oxygen dependent molecular processes implicated in tissue viability and wound healing processes.[5,8,9] Thus, the *db/db* strain represents a useful and cost-effective animal model to investigate developmental and hormonal parameters that occur in the presence of impaired glycemic control and early onset obesity and is bolstered by the clinical observations of improved SpO2 and HbA1c in human subjects following biophotonic therapy. Humans have long sought the healing powers of sunshine exposure for numerous maladies throughout much of recorded history, reflecting the ultimate ancient origins of modern photonic therapy.[2,24–28,30]

Methods

Investigation and targeted review of published resources using the key words identified above, in concert with observation from the authors clinical laboratory were utilized in developing this editorial perspective. For the UV exposure in human subjects,whole blood UV treatment was administered, in a group of healthy subjects with follow-up for up to 120 minutes to one month following completion of the procedure as described previously.[4,5] All subjects signed consent prior to the study. Typical procedures are performed on 60 ml of a patients freshly heparinized blood, diluted with physiologic saline, followed by passage thru a biophotonic exposure apparatus (Azura GHL biophotonic apparatus, consists of a sterile 12 inch quartz mixing chamber with 2 UV-A and 2 UV-Clight sources with stated luminescence of 3.5 W/cm^2 (GE 214-UV light allowing quartz tubes, Quartz Tubes, Grand Lodge MI) where the blood-saline mixture becomes illuminated treated during transit.[4,5] The design of the cuvette was such to ensure that all the blood passing thru would receive the same Quanta of UV exposure, regardless of if it was near the periphery or central canal region of the cuvette. Venous blood was obtained for HbA1c and SpO2 analysis before and exactly two hours after completion of the procedure. HbA1c was determined via affinity chromatography and SpO2 via a pulse oximeter (Pulse MD, Oxilyte Corp). Data were analyzed via Students 't' test for paired comparisons since each subject acted as their own control.[5,28,30] The study was approved by the Institutional Human Subjects Committee and satisfied the Helsinki specifications for human subjects.[4,5]

Results

Miley was among the first to unequivocally document the effects of biophotonic treatment of peripheral blood oxygen saturation in a large group of human subjects over a prolonged duration.[4] In his studies, he applied the UV at 260 nm wavelength for < 30 minutes and recorded blood SpO2 periodically for up to one month or more following the treatments. A summary of his findings is depicted in Figure 1 below and indicates that SpO2 became elevated to near 100% saturation within minutes of UV exposure and remained higher for at least 30 days or more following treatment.

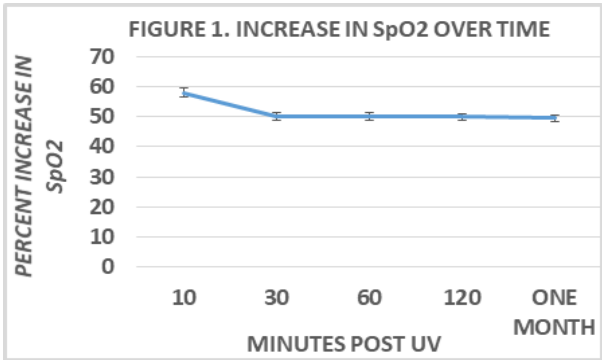

Figure 1 Effect of bio photonic treatment on SpO2 from 10 minutes to one month post treatment. The percentage decrease in SpO2 over 10 minutes to 30 days is depicted. Data are mean ± 1 SEM, n=97 subjects per treatment group. Data are extrapolated from Miley[4] and Tulp et al.[5]

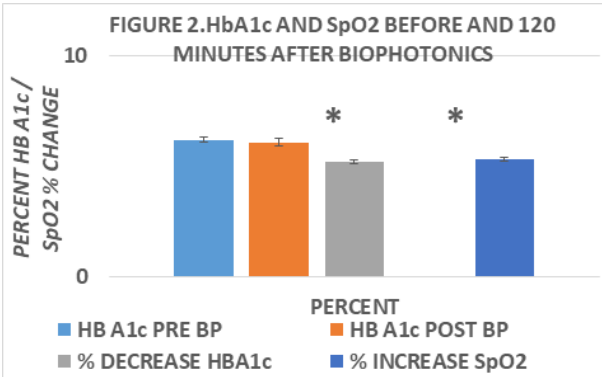

Figure 2 Effects of biophotonic treatment on HbA1c and SpO2 percentages 120 minutes post-treatment. Data are mean ± 1 SEM, n=8 subjects. * P = < 0.05 (pre vs post). [Adapted from[4,5]]

The effects of biophotonic treatment on Hemoglobin A1C prior to and 120 minutes post treatment are depicted in Figure 2 and indicate that the mean HbA1c prior to treatment in a small group of eight subjects averaged 6.25 %, with a range of 5.2 to 7.5 %. In bloods obtained 120 minutes post treatment, HbA1c concentrations decreased by over 5%, to a mean of 6.0 % with a range from 5% to 7%. The percent increase in SpO2 is depicted in the far-right column and indicates that blood SpO2 increased by 5.3% at the two-hour mark, consistent with the observations of Miley on a larger group of subjects (97 vs 8 subjects). Thus, the observations of bio photonic treatment of blood oxygen saturation appear to be consistent and may persist for one month or longer following treatment.

The effects of biophotonic treatment on several metabolic parameters in blood and skeletal muscleare summarized in Tables 1 &

Citation: Tulp OL, Einstein GP. Can biophotonic therapy ameliorate the metabolic sequelae of NIDDM? *Int J Complement Alt Med.* 2024;17(2):97–101. DOI: 10.15406/ijcam.2024.17.00688

Copyright: ©2024 Tulp et al.

2, respectively. In Table 1, fasting glucose and the glycemic responses to a standard glucose tolerance are summarized, and indicate that hyperglycemia and an increased Area under the Glucose curve (AUC) occurred in both the normally fed and the high-fat fed models of the *db/db* mice. Plasma insulin responses were also elevated in the *db/db* animals. Bio photonics treatment resulted in a normalization of both glycemic and insulin responses in both dietary treatments in the *db/db* mice.

In Table 2, metabolic and tissue parameters are summarized take from skeletal muscle preparations in the same animals depicted in Table 1 are shown. Insulin stimulated glucose uptake was decreased in the *db/db* animals and was restored in both dietary models following the bio photonic treatment. The patterns of tissue triglyceride and tissue reactive oxygen species (ROS) content followed a similar pattern to the patterns of glucose uptake, reflective of the differences in glucose oxidation. Measures of tissue glycogen, Coenzyme Q and ATP content were reflective of measures of insulin stimulated glucose uptake in all dietary groups of mice before and after the bio photonics treatment.

Table 1 Effects of photonic treatment on blood glycemic parameters in diabetic mouse models

Treatment group	Parameters				
	Fasting Glucose	**OGT**	**OGT AUC**	**IGT**	**IGT AUC**
WT CONTROL	Normal	Normal	Normal	Normal	Normal
D- *db/db*	Increased	Increased	Increased	Increased	Increased
D- *db/db*+Photonics	Decreased*	Decreased*	Decreased*	Decreased*	Decreased*
D- High Fat Diet	Increased	Increased	Increased	Increased	Increased
DHFD+Photonics	Decreased*	Decreased*	Decreased *	Decreased*	Decreased*

Data are extrapolated from Gong et al; N=7-8 mice per treatment groups. Fasting Glucose concentrations and glycemic responses were determined over a course of 10 weeks. WT, wild type; D-*db.db* = *db/db* mouse strain; OGT, oral glucose tolerance; IGT, Insulin Response to OGT; AUC, area under the glucose OGT or IGT curve; DHFD, Diabetogenic High fat diet. *, p=< 0.05 to 0.01. Extrapolated from[6].

Table 2 Effects of photonic treatment on metabolic parameters in skeletal muscle in diabetic mice

Treatment group	Parameters					
	I+Glc uptake	**TG Content**	**ROS**	**Glycogen**	**CoQ***	**ATP**
WT CONTROL	Normal	Normal	Normal	Normal	Normal	Normal
D- db/db	Decreased	Increased	Decreased	Decreased	Decreased	Decreased
D-db/db+Photonics	Increased*	Decreased*	Increased	Increased*	Increased*	Increased*
D-High Fat Diet	Decreased	Increased	Decreased	Decreased	Decreased	Decreased
DHFD+Photonics	Increased*	Decreased*	Increased	Increased *	Increased*	Increased*

Data are extrapolated from Gong et al; N-4-7 mice per treatment group. Fasting Glucose concentrations and glycemic responses were determined over a course of 10 weeks; WT, wild type non-diabetic control; D-*db/db*, *db/db* T2DM mouse strain; DHFD, Diabetogenic High Fat Diet; *, p=< 0.05 to 0.01; I+Glc uptake is insulin-stimulated glucose uptake; I+Glc ,insulin stimulated glucose uptake; TG ,triglyceride; ROS reactive oxygen species; CoQ ,Coenzyme Q complex; ATP ,Adenosine TriPhosphate; Effects of Insulin and PBMT Photonics on TG, Extrapolated from[6]; uptake is dose related and were found to be additive; *, Changes were unique to CoQ; complexes I, II, III and complex V was unaffected by photonics treatment.

The effects of pO2 on oxyhemoglobin oxygen saturation in whole blood are depicted in Figure 3, including the biochemic responses to both the Haldane and Bohr effects. The Haldane effects typically move the saturation curve to the left, in closer proximity to tissue myoglobin responses, while the Bohr effects results in a rightward shift in the oxygen saturation curve. In contrast, virtually complete tissue myoglobin saturation readily occurs at pO2 concentrations of 10 mm of Hg or less. Biophotonic treatment increased 2,3 DPG binding, thereby facilitating the release and diffusion of oxygen to its tissue myoglobin partner and increasing tissue oxygen availability for cellular oxidative processes. The oxidative process is further enhanced by increasing the formation and intracellular translocation of GLUT4 glucose transporters and improving glucose uptake in peripheral tissues including skeletal muscle and adipose tissue.[7-9, 30,31]

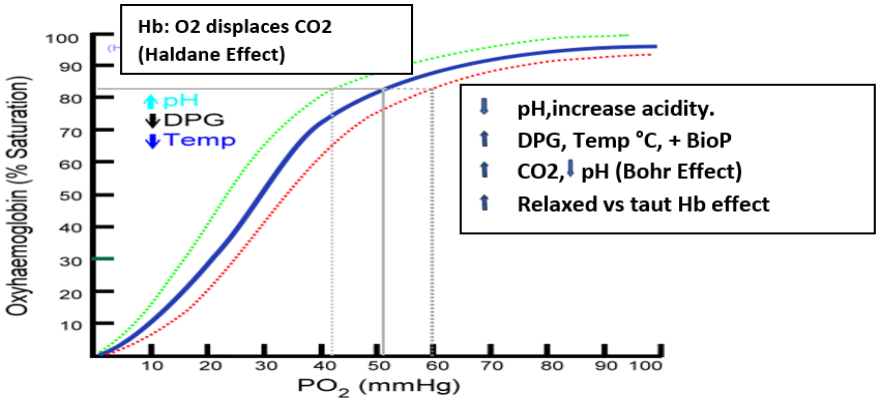

Figure 3 Effects of pH, 2,3-DPG, CO2, Temperature and Biphotonic (BioP) effects on the hemoglobin oxygen saturation curve. DPG = 2,3 diphosphoglycerate; BioP = biophotonics. Modified from.[4,7-9,30,31]

Citation: Tulp OL, Einstein GP. Can biophotonic therapy ameliorate the metabolic sequelae of NIDDM? *Int J Complement Alt Med.* 2024;17(2):97–101. DOI: 10.15406/ijcam.2024.17.00688

Discussion

The physiologic absorption of Quanta of photons derived from light is deemed a prerequisite for multiple aspects of mammalian health, and as such, humans have always instinctively sought daylight for many sorts of illnesses including infectious illnesses, wound healing and other maladies.[1-3,24-28] Of note, UV light irradiation following sunlight exposure has empirically been considered nature's natural cure-all for many kinds of infectious illnesses for many generations of human kind.[4,5] Among the oldest references to the benefits of sun therapy were reported on or before 1500 B.C.[2,3] Although the molecular mechanisms of these photon-mediated, light-derived effects have generally often remained unknown, unconfirmed, or speculative at best, emerging findings now point to a dose related nuclear disruptive element that impedes further local replication of the infectious agent combined with enhancement of immune responses in the UV or sunlight-exposed host.[5,6] According to the laws of photobiology, light absorption requires the presence of a specific photo-acceptor molecule or complex that after photonic excitation could induce or enable the downstream activation of biochemical or physiologic signaling pathways to bring about its desired healthful or other responses.[6,7,36] The blood protein hemoglobin (Hb) is recognized to be an efficient light absorbing photochemical capable of absorbing photons due to its unique electronic configurations which enable it to undergo reversible taut vs relaxed states, and accommodate the efficient transport and release of life-giving oxygen to peripheral tissues. In addition photon application also contributions to elements of blood gas transport, buffering capacity, uptake of 2,3 deoxy diphosphoglycerate (2,3 DPG) and other critical biologic functions.[8,9,10] In addition, the molecular structures of the light absorbing amino acids of cells and tissues makes a further contribution to the efficacy of biophonic treatment. The duration of the photo dissociation effect remains unclear but appears to persist for at least a month or longer following therapeutic biophotonic exposure.[5,6,36]

Because the biophysiologic or molecular mechanism through which biostimulation may deliver its beneficial effects remains speculative, confirmation of the specific molecular targets and subsequent events is unclear. However, the process is dependent on the presence of potential light absorbing elements such as hemoglobin or aromatic structures in the peripheral tissues. Tryptophan, a common amino acid residue to most proteins including the beta chain of hemoglobin, has an absorption band in the 260-290 nm range that can be reached via photonic excitation.[31-33,36] Excitation of tryptophan produces a broad fluorescence centered at 340 nm that extends from 310 to 370 nm, similar to that of tyrosine. Fluorescence from RBCs is centered near 480nm, however, beyond the tryptophan or tyrosine excitable range. While it is possible that tryptophan and/or tyrosine could be excited by the photonic laser, little or no fluorescence would likely become detected given the 310 to 370nm spectra for aromatic amino acids. The fluorescence lifetime reported for tryptophan in proteins shows a small amplitude ~0.2 for the 0.5ns component and the two equally weighted major components with ~2ns and ~5ns lifetime, respectively.[30–33] The difference in emission wavelength and fluorescence lifetime between tryptophan and blood components allows us to rule out tryptophan as the primary but not a secondary source of the 480 nm or broader RBC UV signal.[31,36]

In cases of NIDDM in humans and other mammalian species, significant impairments in glycemic control and management including immune responses develop early in the course of the disease and continue indefinitely thereafter.[9] These metabolic excursions result in alterations in HbA1c levels in peripheral blood, impaired oxygen delivery to peripheral tissues, increases in inflammatory ROS, renal and cardiovascular disorders, delays in wound healing among other pathophysiologic contributions to cardiovascular, renal and neurologic disorders. In animal studies, chronic hyper insulinemia resulted in brain shrinkage and decreased brain DNA content, and impaired nerve conduction velocity, likely a result of chronic neuro inflammatory responses, and are likely contributory to the multiple neurologic symptoms that occur during the pathophysiologic progression of NIDDM in humans.[20,34,35] Thus, any amelioration of the chronic hyperinsulinemia may be presumed to slow the development and progression of the pathophysiologic stigmata of NIDDM. The atypical 2,3 DPG and impaired oxygen displacement that accompanies the HbA1c elevations remains a clinical feature of NIDDM and is a well-established diagnostic marker to monitor diabetes management. Thus, therapeutic measures to improve mean blood glucose concentrations as an approach to lower HbA1c concentrations are a major objective of diabetes management and long-term glucose control.[8,9]

In the Type 2 *db/db* diabetic mouse model, biophotonic treatment of skeletal muscle, a major site of insulin resistance in man and diabetic animal models, restored glycemic responses to an oral glucose tolerance, including insulinogenic responses. Skeletal tissue analysis following biophotonic treatment revealed improved insulin sensitivity, ROS generation and recovery of impaired ATP and glycogen content, suggesting that the effectiveness of biophotonic therapy extends beyond the previously observed responses in both SpO2 and HbA1c in peripheral blood,implicating intracellular events that modulate elements of glucose uptake and metabolism.[6] While measures of GLUT4 transporters were not reported in those studies, application of conventional, established biochemical principles suggest improved availability and activity of GLUT4 transporters to have contributed to the improvements in insulin sensitivity,glucose tolerance,glucose oxidation, and downstream biochemical events that contribute to energy metabolism and storage. Regardless of the molecular events implicated, the biophotonic exposure improved multiple aspects of substrate metabolism at the molecular level in skeletal muscle, a major locus of insulin resistance in NIDDM in man and animals.

Summary and Conclusions

The observation of biophotonics treatment as an effective, non-pharmacologic cost-effective measure to lower HbA1c is a new observation and if applied to a broader population of NIDDM patients, could result in improved oxygenation of peripheral tissues, improved wound healing, and amelioration of the pathophysiologic sequelae of diabetes. Its potential application is supported by clinical and biochemical findings in both humans and animal models of NIDDM. Thus, Photon therapy, via controlled, low dose biophotonics applications at specific, controlled wavelengths and durations, regardless of the biochemical mechanisms involved, represents an emerging, cost-effective theoretical option in the treatment of obesity, NIDDM and glucose intolerant conditions reminiscent of its ancient origins of early humanity.

Conflicts of interest

The authors declare that there have no conflicts of interest associated with this publication.

Acknowledgments

The authors are grateful for the support of the University of Science Arts and Technology, Montserrat for the resources to develop this manuscript.

Funding

None.

References

1. Tulp OL, Einstein GP. Efficacy of Biophotonics adjunct in viral and microbial infections. *J Contemp Med Educ*. 2023;32(12):1–14.
2. Hockberger PE. A history of ultraviolent photobiology for humans, animals, and microorganisms. *Photochem Photobiol*. 2002;76:561–579.
3. Sadraeian M, Zhang L, Aavani F, et al. Viral inactivation by light. *eLight*. 2022;18.
4. Miley G. Ultra-violet blood therapy in acute pyogenic infections. *Proceedings of local branches of the American Societies for bacteriologists, Eastern Pennsylvania Section*. *J Bacteriol*. 1943;45(3):303.
5. Tulp OL, Rizvi SAA, Einstein GP. Effects of biophotonic treatment on hemoglobin A1c and blood oxygen saturation, submitted. *ES J Clin Trials*. 2024;12(1).
6. Gong L, Zou Z, Liu L, et al. Photobiomodulation therapy ameliorates hyperglycemia and insulin resistance by activating cytochrome c oxidase-mediated protein kinase B in muscle. *Aging (Albany NY).* 2021;13(7):10015–10033.
7. Bhagavan NV, Chung-Eun Ha. Function, metabolism, and regulation of organic phosphates in erythrocytes in essentials of medical Biochemistry, 2nd ed. Elsevier Pubs. 2015.
8. Samaja M, Melotti D, Carenini A, et al. Glycosylated hemoglobins and the oxygen affinity of whole blood. *Diabetologia*. 1982;23(5):399–402.
9. Koenig RJ, Cerami A. Hemoglobin A Ic and diabetes mellitus. *Annual Review of Medicine*. 1980;31:29–34.
10. Tulp O L. *Glucocorticoid ablation restores glycemic and thermogenic responses in obesity*. Ch 4 in: Cortisol – between physiology and pathology. Intech open pubs. 2024: pp 73–90.
11. Marette A, Atgie C, Liu Z, et al. Differential regulation of GLUT1 and GLUT4 glucose transporters in skeletal muscle of a new model of Type II diabetes: The Obese SHR/Ntul//-cp Rat. *Diabetes*. 1993;42:1195–1201.
12. Kahn CR. Role of insulin receptors in insulin-resistant states. *Metabolism*. 1980;29(5):455–466.
13. Bukowiecki LJ, Deshaies Y, Collet AJ, et al. Major thermogenic defect associated with insulin resistance in brown adipose tissue of obese-diabetic SHR/N –cp rats. *Am J Physiol*. 1991;261(2Pt 1) E204–213.
14. Marette A, Tulp OL, Bukowiecki LJ. Mechanism linking insulin resistance to defective thermogenesis in brown adipose tissue of obese diabetic SHR/N –cp rats. *Int J Obese*. 1991;15(12):823–831.
15. Dimitriadis G, Leighton B, Parry-Billings M, et al. Effects of glucocorticoid excess on the sensitivity of glucose transport and metabolism to insulin in rat skeletal muscle. *Biochem J*. 1997;321:707–712.
16. Atgie C, Marette A, Desaultels M, et al. Specific decrease in mitochondrial thermogenic capacity in brown adipose tissue of obese SHR/N-cp rats. *Am J Physiol.* 1993;265(6 Pt 1):C1674–1680.
17. Gathercole LL, Morgan SA, Bujalska IJ, et al. Regulation of lipogenesis by glucocorticoids and insulin in human adipose tissue. *PLoS ONE*. 2011;6:e26223.
18. Hauner H, Schmidt P, Pfeiffer EF. Glucorticoids and insulin promote the differentiation of human adipocyte precursor cells into fat cells. *J Clin Endocrinol Metab*. 1987;64:832–835.
19. Tulp OL. Does insulin resistance contribute to the 'unbrowning' or beigeing of brown adipose tissue in obese and obese diabetic rats. *Academia Biology*. 2023;1(1):1–4.
20. Tulp OL. Characteristics of thermogenesis, obesity, and longevity in the LA/Ntul//-cp rat. *ILAR News Journal*. 1990;32(3):133–139.
21. Tulp OL, Awan AR, Einstein GP, et al. Enhanced caloric efficiency contributes to adiposity in LA/N//-cp corpulent rats. *Experimental Biology*. 2021;35:S1.
22. Tulp OL. Effects of aging, phenotype, and carbohydrate feeding on caloric efficiency and adiposity in the LA/Ntul//-cp rat. *Adv Obes Weight Control Manag*. 2021;11(1):5–11.
23. Tulp O, Awan A, Einstein G.Glucocorticoid ablation restores parameters of energy homeostasis in congenic obese LA/Ntul//-cp rats. *Proceedings of the Nutrition Society*.2022;81:e199.
24. Frysh P. Sunlight and Your Health. *WebMD*.2022.
25. Krasnovsky A Jr, Drozdova NN, Ya V, et al. Sun source of photons. Biophotonics of molecular oxygen: activation efficiencies upon direct and photosensitized excitation. *Chin Opt Lett*. 2005;3:S1–S4.
26. Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. *Journal of Clinical Endocrinology and Metabolism*. 1989;68(5):882–887.
27. Hockberger PE. A history of ultraviolent photobiology for humans, animals, and microorganisms. *Photochem Photobiol*. 2002;76:561–579.
28. Rowen R J. Ultraviolent blood irradiation therapy; the cure that time forgot. *Int J Biosocial Med Research*. 1996;14(2) 115–132.
29. White S. *Lange's Basic & Clinical Biostatistics*. 5th ed. McGraw Hill Publishers. 2019.
30. Liebert L, Capon W, Pang V, et al.Photophysical mechanisms of photobiomodulation therapy as precision medicine. biomedicines. 2023;11(2):237.
31. Reeder BJ, Svistunenko DA, Cooper CE et al. The radical and redox chemistry of myoglobin and hemoglobin: from in vitro studies to human pathology. *Antioxidant Redox Sign*. 2004.6(6):954–966.
32. Pan L, Wang X, Yang S et al. Ultraviolet irradiation dependent fluorescence enhancement of hemoglobin catalyzed by reactive oxygen species. *PLoS ONE.* 2012;7(8):e44142.
33. Patwardhan RS, Checker R, Deepak Sharma D, et al. Involvement of ERK-Nrf-2 signaling in ionizing radiation induced cell death in normal and tumor cells. *PLoS One* . 2013;8(6):e65929.
34. Tulp OL. Determining the effect of high carbohydrate diets on brain composition and senescence in aging hyperinsulinemic obese la/ntul//-cp rats. *ChIn:Novel Research Aspects in Medicine and Medical Science*. 2023;2(6):159–176.
35. Tulp OL. The epigenetic expression of obesity and its metabolic sequelae contribute to brain senescence and decreased longevity in aging obese la/ntul//-cp rats. *ES J Public Health*. 2023;4(1):1018.
36. Tulp OL, Rizvi AA, Einstein GP. Effects of biophotonic treatment on hematologic parameters. Preprints.org.