Non-Thermal 635nm Low-Level Laser Therapy in Pre-Diabetes and Obesity Management.

An in-house 10 week study of 140 pre- diabetic and pre-obese patients with 6 monthly follow-ups 2015 - 2020

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Background

Pre-Diabetes and pre-obesity often go hand in hand. Diabetes mellitus (DM) is a chronic condition that can alter our carbohydrate, protein, and fat metabolism. It is caused by the absence of insulin secretion due to either the progressive or marked inability of the β-Langerhans islet cells of the pancreas to produce insulin, or due to defects in insulin uptake in the peripheral tissue. DM is broadly classified under two categories, which include type 1 and type 2 diabetes[i].

Body mass index has a strong relationship to diabetes and insulin resistance. In obese individuals, the amount of non-esterified fatty acids (NEFA)[1], glycerol, hormones, cytokines, proinflammatory markers, and other substances that are involved in the development of insulin resistance, is increased[ii].

The pathogenesis in the development of diabetes is based on the fact that the β-islet cells of the pancreas are impaired, causing a lack of control of blood glucose. The development of diabetes becomes more inevitable if the failure of β-islet cells of the pancreas is accompanied by insulin resistance. Weight gain and body mass are central to the formation and rising incidence of type 1 and type 2 diabetes[iii].

In conclusion, new approaches in managing and preventing diabetes in obese individuals must be studied and investigated based on the facts. True Non-Thermal Low Level Laser Therapy (NTLLLT) may form part of the solution.

The association between type 1 diabetes and weight gain was first investigated by Baum et al in 1975. The Baum et al study suggested that there was an association related to overfeeding or to hormonal dysregulation[iv].

Overweight and obesity are defined by an excess accumulation of adipose tissue to an extent that impairs both physical and psychosocial health and well-being[v]. Obesity is considered a health disaster in both developed and developing countries[vi].

[1] Non-esterified fatty acids (NEFA) are molecules released from triglycerides by the action of the enzyme lipase and are transported in the blood bound to albumin. They contribute only a small proportion of the body's fat; however provide a large part of the body's energy. Measurement of NEFA is important in diabetes where insulin deficiency results in the metabolism of fat. Levels are also frequently increased in obese patients.

The increased prevalence of obesity these days has drawn attention to the worldwide significance of this problem[vii]. In the US, for example, approximately two-thirds of the adult population is considered to be overweight or obese. Similar trends are being noticed worldwide[viii]. Obesity is linked to many medical, psychological, and social conditions, the most devastating of which may be type 2 diabetes. At the start of this century, 171 million people were estimated to have type 2 diabetes, and this figure is expected to increase to 360 million by 2030[ix]. The figures from the World Health Organisation show that About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.6 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades[x]. A comparison of the two sets of statistics shows just what a combined problem these two conditions combined are. The Pharmacoeconomics, not to mention the associated costs on health services is staggering. In 2016 the estimated burden of diabetes on healthcare infrastructure was 825 Billion USD[xi]. There are no published figures for 2020, it is estimated to be in excess of a trillion USD.

Since the time of the commencement of the is study NTLLLT has become more sophisticated and, according to research and FDA accreditation, more efficacious. The organisation who's lasers were used in this research have also brought to market green 532nm NTLLLT for circumferential reduction and temporary reduction in the appearance of cellulite. The circumferential reduction study reported 25% improvement in results in 25% less time when compared to their red 635nm study data. All studies were Level One (510k), so were placebo controlled, double blind, randomised and multi centre.

The Study

The study enrolled 140 men and women between the ages of 35 to 65 with a body mass index (BMI) of 27 to 40. Participating subjects were randomised in a double-blind fashion to receive NTLLLT (N=70) or sham LED treatment (N=70). All study participants, in conjunction with a dietician, to maintain a mild ketogenic diet. All were given the same three times a week moderated exercise plan and were required to keep a diary. Bloods were monitored daily via WhatsApp feedback and weekly full blood counts were taken to include sugars, cholesterol, liver and kidney function. Fluid intake was also measured. All subjects were further instructed to continue all medications, and to kept all normal medical appointments. This study was carried out with the knowledge and agreement of participants, general medical attendants, and where necessary any specialists they were under the care of.

All subjects involved in this study were recommended and referred by their medical team and had to be pre-diabetic and pre-obese or obese and on no medication for these conditions.

Treatment device.

The NTLLLT energy device is non-invasive and is cleared by the FDA for use as a non-invasive aesthetic dermatological treatment for reducing the circumference of hips, waist, and thighs and is manufactured by Erchonia Corporation USA. The NTLLLT device consists of four

independent diodes that are positioned 120 degrees apart and tilted at a 30-degree angle. A fifth diode is positioned at the centreline.

The 17mW of red 635nm of laser light emitted from each diode is collected and processed through a proprietary lens that redirects the beam with a line refractor. The refracted light from each diode is bent into a random spiralling circle pattern that is independent of the other diodes. These overlapping patterns ensure total coverage of the target treatment area. The total amount of energy delivered to the skin during each treatment as stated in the FDA clearance was 3.94J/cm^2. Evidence however suggests that this is not relevant as the laser delivers photonic energy via electromagnetic energy transfer.

Procedure.

Each subject was randomised to receive 20 active or sham treatments twice per week, equally spaced apart with the NTLLLT energy device over a 10 week period. Both the active and sham devices have the same physical appearance and emit light when activated that is indistinguishable to both the subject and the administration investigator. All subject had a moderated exercises session after each treatment and another on a day of their choice. Nutritional plans were also moderated for compliance.

Study assessments.

The circumference of each participant was measured using a flexible tape measure pre and post each application at 3 points, the base of the circumference at sternum, the circumference at the umbilicus, and again at the trochanter. For accuracy at remeasuring post treatment a skin marker was used under the tape at a number of points so the measurements re duplicated. These point were recorded at baseline to ensure that subsequent measurements were obtained at the same location. All measurements were performed by a member of the investigative team not involved in performing the actual treatments. All subjects were photographed from front, sides and back with hands on head

The primary outcome measure was the accumulated BMI from the number of subjects, and the total numbers were seen to achieve a decrease.Individually the three combined measurement points after each session were recorded. Blood glucose was also measured each week, along with weight and other variables such as sleep quality and energy levels. Secondary outcomes assessed at the completion of the study included changes in BMI, associated diabetes risk, obesity levels and several subjective ratings, which measured subject attitudes about overall satisfaction with their results and improvements in the appearance.

All study assessments were performed at baseline, at the completion of treatment, and two weeks post-treatment. Following the baseline physical examination, a blinded investigator noted any changes in existing skin condition including scars, cellulite, stretch marks, discoloration, stria, dimpling, and skin quality and elasticity following treatment. Details about food and drink consumption, physical activity, and adverse events for each subject

were recorded daily. Further follow ups were recorded every 12 weeks primarily for the first 18 months from inception, then extended over the 5 year period. The study is now concluded.

Ethics.

The protocol used in this study adhered to the Good Clinical Practice guidelines and were approved by the local ethics committee in April 2015. The study was overseen by colleagues in the diabetes assessment unit at the local university hospital Informed written consent was obtained from each subject prior to participation in any study-related activities.

Laser Diode Placement

The diodes are place over the lateral flanks and around the umbilical area. The treatment runs for 20 minutes and is then repeated for another 20 minutes, with the participant repositioned. A more comfortable method for heavier subject is for them to lay on their side and the diodes positioned accordingly to cover half of the midsection, the subject then repositions to the other side.

Rational

To find an alternative to the current interventions for diabetes, obesity and associated conditions, and to reduce the overall economic burden and improve quality for life and outcomes for sufferers.

Baselines and Results.

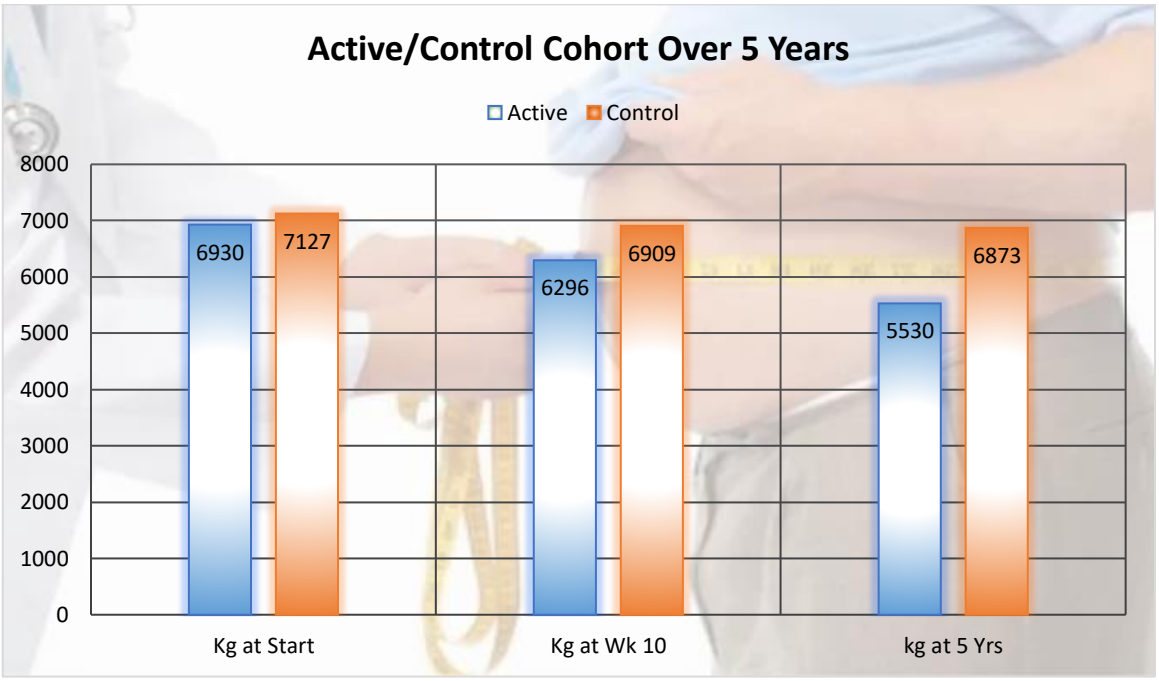
Gender	*Female*	*Male*	*Group*	
Average Age	47.91 (N=35)	49.48 (N=35)	N=70	
Average Weight	93Kg	105Kg	198Kg	Combined
Average Height	171cm	176cm		Constant
Average BMI	31.8	33.9	65.7	Combined
Average Cholesterol	5.05	5.77	10.82	Combined
Total Cohort Weight	3255Kg	3675Kg	6930Kg	Combined
		Average	99Kg	

The above chart is the active laser group at baseline.

Gender	*Female*	*Male*	*Group*	
Average Age	41.93 (N=33)	49.16(N=37)	N=70	
Average Weight	96Kg	107Kg	203Kg	Combined
Average Height	172cm	179cm		Constant
Average BMI	32.4	33.4	65.87	Combined
Average Cholesterol	5.29	5.73	11.02	Combined
Total Cohort Weight	3168Kg	3959Kg	7127Kg	Combined
		Average	101.81Kg	

The above chart is the control group at baseline.

Throughout the study all participants had their blood pressure, cholesterol and blood sugars monitored. Changes in behaviour were also taken into account as were sleep patterns, changes in energy levels and general skin appearance. A glycated haemoglobin test (HbA1c) was taken every 12 weeks.



The above graph is an expression of the main outcomes measure. Making sense of the graph at week 10 and year 5 in terms of clinical relevance is important, as is cholesterol, stabilisation of bold sugars and the numbers ho progress to a diagnosis of diabetes.

Gender	*Female*	*Male*		*Group*	
Active Cohort Stats	(N=35)	(N=35)		N=70	
Average Weight Inception	93Kg	105Kg		198Kg	Combined
Average Weight Wk10	84.9Kg	94.9Kg		179.8Kg	Combined
Average BMI Inception	31.8	33.9		65.7	Combined
Average BMI Wk10	29	30.6		59.6	Combined
Average Cholesterol Incept	5.05	5.77		10.82	Combined
Average Cholesterol Wk10	4.03	4.52		8.55	Combined
Total Cohort Weight Inception	3255Kg	3675Kg	Average	6930Kg 99Kg	Combined
Total Cohort Weight Wk10	2973Kg	3323Kg	Average	6296Kg 89.9Kg	Combined

As can be seen above, NTLLLT combined with a modified nutritional plan and exercise appears to have a positive effect on outcomes. The below charts looks at the control group.

Gender	*Female*	*Male*		*Group*	
Control Cohort Stats	41.93 (N=33)	49.16(N=37)		N=70	
Average Weight Inception	96Kg	107Kg		203Kg	Combined
Average Weight Wk10	93Kg	103.8Kg		196.8Kg	Combined
Average BMI Inception	32.4	33.4		65.87	Combined
Average BMI Wk10	31.4	32.1		63.5	Combined
Average Cholesterol Incept	5.29	5.73		11.02	Combined
Average Cholesterol Wk10	4.97	4.91		9.88	Combined
Total Cohort Weight Inception	3168Kg	3959Kg	Average	7127Kg 101.81Kg	Combined
Total Cohort Weight Wk10	3069Kg	3840.6Kg	Average	6909.6Kg 98.7Kg	Combined

As this is a simple inhouse study, the information shared would benefit from more testing and a full RTC. The lead researcher and his team maintained strict protocols throughout this study. At the end of the 10 weeks all the subjects in the active protocol had undergone 4 weeks of further monitoring in relation to their blood glucose levels and 69 of them no longer presented as a diabetes risk. However, the control group all remained on the diabetes index as being at risk at week 10 +4. All subjects were encouraged to follow their established exercise routine and foster their nutritional habits. Follow-ups were taken every 6 months until July 2020.

See below id, endpoint data and discussion.

Gender	*Female*	*Male*		*Group*	
Active Cohort Stats	(N=35)	(N=35)		N=70	
Average Weight Inception	93Kg	105Kg		198Kg	Combined
Average Weight Wk10	84.9Kg	94.9Kg		179.8Kg	Combined
Average Weight at Exit	77Kg	81Kg		158Kg	Combined
Average BMI Inception	31.8	33.9		65.7	Combined
Average BMI Wk10	29	30.6		59.6	Combined
Average BMI at Exit	26.3	26.1		52.4	Combined
Average Cholesterol Incept	5.05	5.77		10.82	Combined
Average Cholesterol Wk10	4.03	4.52		8.55	Combined
Average Cholesterol at Exit	3.2	3.5		6.7	Combined
Total Cohort Weight Inception	3255Kg	3675Kg	Average	6930Kg 99Kg	Combined
Total Cohort Weight Wk10	2973Kg	3323Kg	Average	6296Kg 89.9Kg	Combined
Total Cohort Weight at Exit	2695Kg	2835Kg	Average	5530Kg 79Kg	

70 pre-diabetes subjects entered the active cohort, and only 2 went on to develop diabetes but remained healthy and continue to use the programme. Below are the final outcomes of the control group.

Gender	*Female*	*Male*		*Group*	
Active Cohort Stats	(N=33)	(N=36)		N=69	
Average Weight Inception	96Kg	107Kg		203Kg	Combined
Average Weight Wk10	93Kg	103.8Kg		196.8Kg	Combined
Average Weight at Exit	91Kg	107.5Kg		158Kg	Combined
Average BMI Inception	32.4	33.4		65.87	Combined
Average BMI Wk10	31.4	32.1		63.5	Combined
Average BMI at Exit	26.3	26.1		52.4	Combined
Average Cholesterol Incept	5.29	5.73		11.02	Combined
Average Cholesterol Wk10	4.97	4.91		9.88	Combined
Average Cholesterol at Exit	4.1	4.9		9	Combined
Total Cohort Weight Inception	3168Kg	3959Kg	Average	7127Kg 101.81Kg	Combined
Total Cohort Weight Wk10	3069Kg	3840.6Kg	Average	6909.6Kg 98.7Kg	Combined
Total Cohort Weight at Exit	3003Kg	3870Kg	Average	6873Kg 99.6Kg	Combined

In the control group, 65 went on to develop diabetes and one died as a result of complications related to diabetes. Over time, their weight rose again. The female members of the group maintained a reduced weight and cholesterol levels. All subjects continued with exercises and a reasonable diet. The men in this group slowly relapsed back to their previous lifestyle. All of the male cohort in this group developed diabetes.

Discussion

There is a growing body of research showing the benefits of NTLLLT in the management of the human fat cell, pain management and neurological disorders; but yet there is no substantive research into the benefits of this technology in the management of obesity and diabetes. Weight contributed to rheumatoid arthritis, heart disease, kidney disease, osteoarthritis, and is now a contributory factor in problems associated with the coronavirus. There are well recorded positive side effects associated with the use of NTLLLT[xii], these effects need to be exploited as in a more recient paper by Connor et al[xiii] into the use of 405, 532 and 635nm lasers and there affect on Mesenchymal Stem Cells (MSC) and renal fibrosis. In the context of diabetes research, MSC have been used to generate insulin-producing cells[xiv]. This is a simple inhouse study exploring the use of NTLLL at 635nm in pre-diabetes/pre-obese patients; can we do anything to reduce the potential development of diabetes?

Conclusion

Diabetes is potentially a life limiting condition and fraught with many comorbidities. Patients may go on to develop issues with blood pressure, kidneys, neuropathies, amputations; or the list is practically endless. This study, though inhouse, has followed best practice in terms RTC. It is not perfect, no doubt there are many holes one could find in it. This said, the evidence presented speaks for itself. NTLLLT may have a place in the armament of treatments used in prevention and control, for what is one of the world's biggest health issues. Sixty-five out of seventy participants in the study who were pre-diabetic and pre-obese turned their lives around in 10 weeks. Over a 5 year period they continued to improve and maintained the good habits they had formed on the study. They were no longer a diabetes risk and were not obese, they all had good cholesterol levels and no blood pressure issues. They are no longer a burdon on the healthcare system. Although further study data is required, NTLLLT could have general long lasting benefits for diabetes, obesity, and health.

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