Review Article

A Review on Experimental and Clinical Studies of Complementary and Alternative Medicine in Prediabetes

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ABSTRACT

Prediabetes or latent phase of Type 2 Diabetes mellitus (ICD 10- R73.03) is associated with increased risk of progressing to manifestation of diabetes. Complementary and alternative medicine (CAM) has a long history of use in certain parts of the world and has gained increasing interest over the last decades globally. CAM includes both Pharmacological and Non-pharmacological treatment modalities and these are sought for management of most of the diseases including metabolic disorders, especially for long term care. Multiple studies have shown the effectiveness of CAM interventions in management of Prediabetes. This review collates and summarises current (as on May 2020) published literature on CAM as a management strategy for Prediabetes. We included articles in English language from PubMed and Scopus databases using appropriate free keywords and MeSH terms related to the topic. Search strategy yielded articles of which few were unrelated to the topic and few were on Diabetes mellitus of both types. In the process of review, we tried to categorise each of the available mode of treatment as pharmacological and non-pharmacological management and collated the available evidence on the same.

Keywords: Acupuncture, Ayurveda, CAM, Exercises, Herbal medicine, Prediabetes, Yoga.

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INTRODUCTION

Prediabetes is a stage in which the blood glucose levels will be fiddling above the normal physiological level, but lower compared to threshold of diabetes. It is a phase associated with increased risk of progressing to diabetes referring to early states of disturbance in the equilibrium of glucose including impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Limiting the number of people progressing to full-fledged disease by controlling and managing judiciously at early stages of prediabetes is one of the key strategies in reducing the global impact of diabetes[1,2].Few studies suggest for the prevalence of prediabetes in subjects who were previously non-diabetic patients with a recent Transient Ischemic Attack(TIA) or stroke ranges from 23 to 53%[3].The regimens with reassuring results that are prescribed and designed to control progression of the disease may not be accessible economically or may be associated with toxicity or may be associated with difficulty in compliance with the regimen[4].Diagnosis of prediabetes stage remains ambiguous with few researchers acknowledging HbA1c as the tool while others have disapproval for the same and some opine that population specific range of HbA1c must be fixed after conducting micro- and macro-vascular complications, long-term prospective studies[5]. One study considers 1hour post prandial glucose of ≥155mg/dl as a novel biomarker for diagnosing prediabetes[6].It can be used as a tool, only to detect individuals with risk of Diabetes mellitus whereas for researches on prediabetes and interventions it is not a recommended tool[7]. Life style changes including changes in diet and increase in regular physical activity are the first line of management in prediabetes and type II Diabetes and it is claimed that it delays progression of the disease[8]. Despite the perception amongst the population of considering contemporary medicine as most efficacious, the practice of complementary and alternative systems are still prevalent. These are usually sought for when the health problem requires long term management.

Complementary and alternative systems of medicine(CAM) include a comprehensive range of therapies like Ayurveda, yoga, spiritual therapy etc [9]. A wide array of CAM are being used with varying success in management of diabetes mellitus. As diabetes mellitus need immediate treatment and life style interventions and other complementary therapies mainly helps in management of the disease in long term, we considered prediabetes for the review as lifestyle management and other interventions are solid management plan for it.

Methodology

This narrative review is based on the PubMed and Scopus electronic database search of literatures. We searched for articles in English language till May 2020. The search terms included the MeSH –Complementary and alternative

medicine and prediabetes. Randomised trial protocols and diagnostic articles were excluded from the study and remaining articles that exclusively published on complementary and alternative treatment modalities were included in the study.

Pharmacological intervention in prediabetes

Herbs (Chinese medicine, Ayurveda and other systems in Prediabetes)

Gosha-jinki-gan, a polyherbal formulation is proven to reduce serum insulin levels in obese, prediabetic zucker rats when administered for 12 weeks, but there was no significant reduction in serum insulin levels in lean, zucker rats[10].Hyperinsulinemia was induced in Male Sprague-Dawley (SD) rats due to chronic feeding of 10% glucose in drinking water daily. Ethanolic crude extract of *Sorbus decora C. K. Schneid.* (Rosacea) administered for two weeks showed improvement in the insulin sensitivity in a prediabetic insulin resistant model[11]. Extract of *Vitis vinifera* showed improvement in prediabetic mouse model induced with peripheral neuropathy[12]. Polyphenol enriched cocoa extract (PECE) was administered to wistar rats along with the combination of normal rat diet and 10% sucrose. The effect of PECE group was compared with groups which received only normal diet and other with diet and 10%sucrose only and results proved that PECE has potential to ameliorate Homeostasis model assessment – insulin resistance (HOMA-IR) as well as lower hepatic insulin sensitivity (LISI)[13].

In a randomised double blind placebo controlled trial conducted on 240 participants fulfilling at least one of the three prediabetes criteria as per American diabetic association, curcumin was administered for a period of 9 months. The study showed that 0% in curcumin treated and 16.4% patients in placebo group patients progressed to type 2 diabetes[14].In another similar study involving 20 subjects, 500mg/ day of cinnamon and placebo was given to individuals with fasting plasma glucose in the range of 100-126mg/dl over 12 weeks[15]. Cinnamon group showed significant reduction in the glucose levels. In another study conducted using cinnulin (Water soluble extract of cinnamon) over a period of 12 weeks on 22 subjects with metabolic syndrome and prediabetes proved significant decrease in FBG (-8.4%: 116.3 +/- 12.8 mg/dL (pre) to 106.5 +/- 20.1 mg/dL (post)[16]. Cinnamon is also proven to increase working memory in prediabetics of ≥60years compared to other culinary spices like ginger[17].A similar study proved the effectiveness of Turmeric (Curcuma longa) in enhancement of working memory in post prandial state. 48 prediabetic, untreated subjects were randomised and divided into three groups-two groups with cinnamon and turmeric separately and third group was administered with combination of both. Working memory increased with turmeric but not with Cinnamon[18].Aqueous extract of mulberry leaves were administered to 42 eligible subjects with FBG in the range of 100– 125 mg/dL in a double blind randomised clinical trial setting of 4 weeks duration. The study did not show any significant differences in the baseline characteristics, including glycaemic control parameters, anthropometric measurements, and serum lipid profiles, between the treatment and placebo groups[19]. A narrative review on *Moringa olifera* provides evidence that it is a promising herb in the management of prediabetes and diabetic conditions[20]. A traditional, Chinese hypoglycaemic herb identified as Tianqi Jiangtang was evaluated for its prophylactic potential in diabetes in 194 drug naive individuals with Fasting Plasma Glucose level lower than 7.0 mmol/L and a glucose level between 7.8 mmol/L and 11.1 mmol/L after a two-hour OGTT and individuals were administered 4.8gm of the herb in divided dose for 3 to 12 months showed 56% efficacy of the herb in controlling the progression to T2DM[21]. A randomised trial was conducted on 71 prediabetic subjects and administered with Jiangtang Xiaozhi, a Chinese herbal medicine for 16 weeks. Subjects did not show statistically significant results in reduction of any of the parameters assessed at baseline and after 16 weeks of study, yet there was some reduction in the fasting insulin levels[22].

A case controlled study was done on 116 prediabetic patients randomly assigned into two groups of control and treatment group administered with Qiyao Xiaoke Capsule (QXC). Though there was decrease in the FBG, 2h PBG and HbA1c, the results were not significant statistically[23]. Tang-Nai-Kang (TNK) a mixture of extracts from five herbal plants: *Fructus Ligustri Lucidi* (Oleaceae), *Spica Prunellae Vulgaris* (Labiatae), *Saururus chinensis* (Saururaceae), *Psidium guajava* (Myrtaceae) and *Radix Ginseng* (Araliaceae) was administered for 7 consecutive weeks in SHR/cp rats. A group administered with high doses of TNK reduced serum blood glucose and improved insulin sensitivity[24]. Diabetic amelioration potential of persimmon leaf extract (PLE) was determined by assessing saliva, serum and urinary samples for their proteomic changes. There was changes seen in salivary proteomic profile that can be considered as potential protein signature[25].

Anti-diabetic potential of bitter gourd (*Momordica charantia L.*) in the form of dietary supplement was assessed in prediabetic population of Tanzania and subjects were administered with 2.5gm of powder of bitter gourd per day for 8 weeks duration including the wash out period of 4 weeks. Study showed considerable reduction in FPG levels compared to the baseline[26]. Emanuel and colleagues did a meta-analysis on potential of *Momordica charantia L* in lowering glycaemic parameters in n prediabetes and T2DM. This study finally included 13 independent studies and provided low evidence for glycaemia lowering activity of herb *Momordica charantia*[27]. Despite studies showing the effect of bitter melon in lowering glycaemic parameters, it remains a controversy due to few studies that claim its ineffectiveness on the same[28].A quasi controlled pre-test and post-test study was conducted in Indonesia on 16 elderly, prediabetics and administered with extract of celery (*Apium graveolens Linn.*) capsules. The study was conducted using 250mg three capsules in a day for 12 days

duration and showed reduction in the plasma pre-prandial glucose by 9.8% in the recruited subjects[29]. In a small cohort pilot study conducted by Zhu et al demonstrated a polyherbal antioxidant formulation, Glucovita administered for a period of 12 weeks reduced plasma glucose levels and Glycosylated haemoglobin significantly in elderly subjects recruited for the study[30].

A double blind, placebo controlled trial was conducted by an Investigational Drug Services on 45 prediabetic volunteers administered with two products of *Aloe vera* namely Aloe product 1, UP780, and aloe product 2, Q Matrix or AC952 and placebo capsules in placebo group. The study did not show any significant change in glycaemic parameters between two groups from baseline to end of the study[31].Dick et al conducted a meta-analysis on effectiveness of *Aloe vera* and its compounds in lowering the fasting blood glucose and HbA1c in prediabetes and diabetic population. Results support oral usage of *Aloe vera* significantly reduces FBG (46.6 mg/dL) and HbA1c (1.05%)[32]. Zhang et al conducted a meta-analysis on the effectiveness of *Aloe vera* in Prediabetes that involved 5 studies for meta-analysis and it revealed a limited, statistically significant evidence in flavouring *Aloe vera* in reducing blood glucose parameters[33].

Non-pharmacological interventions in prediabetes

Yoga and other mind body practices

A short term yoga based life style intervention was conducted on 896 subjects for 10 days. The study showed a reduction in mean baseline FPG level of 133.1 (± 47.98) to 121.19 (± 40.56), thereby significantly reducing FPG[34]. Ramamurthy and colleagues conducted a meta-analysis of RCT and non-RCT studies to check the effectiveness of yoga in patients with high-risk T2DM i.e prediabetic population, especially to determine if yoga delays progression to full-fledged T2DM in comparison to exercise. The study concluded that yoga plays a potential role in ameliorating the diabetic profile parameters like Fasting blood glucose, post prandial blood glucose and glycosylated haemoglobin[35]. Diabetic yoga protocol(DYP) was employed on 37 prediabetic female subjects diagnosed as per IDRS with scores ≥60 % and grouped into two, of which one group performed DYP for 3 months (n = 22) and the others were considered as control (n =15). The study showed a significant reduction in HbA1calong with other glycaemic parameters, lipid profile levels compared to the control group[36].A randomised control trial was conducted on 29 prediabetics and advocated 3 month yoga program after baseline assessment of outcome parameters like Malondialdehyde, glutathione, vitamin C, vitamin E, Superoxide dismutase, plasma glucose, glycated haemoglobin, BMI, waist circumference, waist-to-hip ratio and blood pressure and Yoga sessions of 75-90 minutes with two days breakup during weekends was employed for three months. Yoga intervention in prediabetes significantly reduced BMI, waist circumference, systolic blood pressure and fasting plasma glucose levels[37].

The effect of Group lifestyle interventions was assessed on 261 volunteers in a randomised clinical trial who had HbA1c in the range of prediabetic and BMI ≥ 24 kg/m^2.Diabetes prevention program- group lifestyle intervention was administered for 12 months comprising of 22 sessions based on social cognitive theory and focuses on behavioural skills and remarkably reduced the HbA1c [38]. A randomised clinical trial to determine the impact of 12 weeks yoga program on Quality of life(QoL) and Indian diabetes risk score(IDRS) in Diabetics and prediabetics young Indian adults and results showed significant attenuation in scores of QoL and IDRS[39].

Stress management using mindfulness-based stress management program combined with diabetes (MPD) risk-reduction education versus a conventional diabetes risk-reduction education program was conducted among African American adults with prediabetes. The program was administered for 8 weeks for 2.5 hours with a half-day retreat and six-monthly boosters and showed reduction in HbA1C in both groups along with decrease in stress level in MPD group[40].

Exercise video games and standard physical exercise

A randomised control trial was conducted to assess the differential effect of 12 weeks of standard physical exercise like treadmill, cycling, and exercise video game (EVG) in individuals with elevated HbA1c ranged from 5.7% to 6.4%. By the end of 12 weeks, it was shown that participants exposed to EVG had an average 2% reduction in HbA1c compared to a 0.6% reduction in Standard and Control groups. Perhaps EVG is more enjoyable and thus becomes compliant than the regular exercise[41].

In a study reported by Halliday et al, effect of participation in a social cognitive theory (SCT)-based Resistance Training (RT) program on dietary patterns and other health behaviours, showed that these influence on the lifestyle and would reduce the progression of prediabetes stage to full-fledged diabetic stage[42].

Diet and prediabetes

Wien et al conducted a randomised control trial of 16 weeks duration to prove the relevance and importance of almond-enriched ADA diet in the context of nut-free ADA diet guidelines to test the hypothesis that it improves measures of insulin sensitivity and other CVD risk factors individuals with prediabetes. Almond intervention was associated with lower fasting glucose levels and this encourages the emerging researches on gut-brain-liver axis that increases insulin sensitivity in the liver[43]. Dietary supplementation with Delphinol, delphinidin-rich maqui berry extract was administered for 3 months in 31 subjects with moderate glucose intolerance. Study revealed that there was remarkable reduction in glycosylated haemoglobin levels at the end of 3 months and it proved to have a promising potential in regulating glucose metabolism[44]. A dietary supplement 5-aminolevulinic acid (5-ALA) when administered for 12 weeks in randomly assigned subjects in a placebo controlled trial on

prediabetic with HbA1c range of 5.8%-7.0% showed amelioration of 2 hours post-OGTT glucose levels compared to those not taking the supplement[45] and also improved the mood and coping ability in prediabetic individuals when administered over 12 weeks[46].

Acupuncture and Prediabetes

In a study conducted in 2018 by Zhao et al, 100 prediabetic patients were grouped into three intervention arms ie 35 subjects in first group with standard metformin, 35 subjects in second group with acupuncture and 30 subjects in third group with lifestyle interventions. The acupuncture points were punctured using filiform needles for about 2 min every 5 min during 30 minutes in a prescribed pattern and conducted once in every other day for 12 weeks. The levels of FBG, 2 h-PBG, HbA1c were decreased significantly in both treatment and acupuncture group showing their effectiveness in preventing progression of prediabetic to diabetic state[47]. Catgut embedding for done in 43 subjects for 3 months in prediabetic subjects and another group of 43 subjects were maintained as control. Though there was some improvement in diabetic indices, they were not significant statistically and also associated with post-operative reactions like dietary inhibition, malaise and abnormal feeling without blocking the treatment [48].

Combination therapies/ interventions in prediabetes:

A pilot, parallel, randomized controlled trial that combined Fitness, Relaxation, and Eating to Stay Healthy (FRESH) therapies administered to female, African-American, history of HbA1c 5.7-6.4%, and a BMI ≥25 for 6 weeks duration demonstrated inclination towards improvement in healthy eating and cooking habits without remarkable changes in weight, blood sugar, or other biometric measures were observed[49]. A randomised controlled trial involving 80 prediabetes participants divided into two groups using a combination therapy using 42 doses of decoction of Chinese herbal medicine administered over 24 weeks duration, 21 sessions of acupuncture and 6 lectures of lifestyle intervention and exclusively life style intervention in the control group is registered in Chinese clinical registry and trial is still ongoing[50]. Potential of Ayurveda and yoga individually and in combination was evaluated in prisoners freshly diagnosed with more than 100mg/dl of FBG. The study involved three groups which comprised yoga with Ayurveda herbal juices, yoga and no intervention. Groups with Ayurveda and yoga combination and no intervention showed a difference of 0.09 with baseline HbA1c and clinically and statistically significant[51].

Limitations

In few studies included in the paper, there was no follow up after the prescribed duration of the trial, conducted in the controlled environments where the influence of the confounding factors present in routine life were not included and small sample number thus the analyses was not powered appropriately. We considered articles on CAM published in PubMed and Scopus databases only and did not consider other databases and sources of grey literature as well. Articles in English language alone were included and few articles which did not retrieve full text and in other languages were not included in the study. In the databases search, we found more studies involving different herbs (Pharmacological) than other modalities of treatment.

FUTURE PROSPECTS & CONCLUSION

CAM includes an extensive mode of treatments and relevance and efficacy of these in management of prediabetes and controlling glycaemic parameters are to be designed appropriately using whole system research designs. Case controlled studies that compare these therapies with the complementary medicine are to be encouraged to prove the equal and parallel effectiveness of these CAM therapies in treatment of prediabetes and preventing the progression to next stage of full-fledged T2DM and its complications.

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