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Can Curcumin Be Effective In Managing and Preventing Major Complications For Type 2 Diabetics Or Even Prevent The Onset of Type 2 Diabetes in Pre-diabetics?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not curcumin can manage and prevent major complications for type 2 diabetics or even prevent the onset of type 2 diabetes in pre-diabetics.

Study Design: Review of two English articles and one English/Italian article. Two were double-blinded, randomized control trials (RCTs) and one was a controlled, therapeutic protocol registry in which subjects were allowed to choose to be in the experimental group. All were published after 2012.

Data Sources: Both RCTs and the controlled, registry study were found through PubMed.

Outcomes measured: This review assessed whether curcumin could delay the progression of prediabetes to diabetes, prevent the onset of obesity and reduce the degree of vision loss in type 2 diabetics. The following were measured by tallying the number of subjects who developed type 2 diabetes, measuring waist circumference, and comparing scores on the Snellen eye chart respectively.

Results: With regards to preventing the onset of type 2 diabetes, the ARR demonstrated that there was a 16% absolute decrease in the risk of developing it, but it is also not a large risk reduction since most of the subjects on placebo did not progress to type 2 diabetes anyway. The difference in the number of subjects who progressed to type 2 diabetes was still statistically significant. The difference in waist circumference was not statistically significant, but only subjects taking curcumin had any reduction in their waist circumference. The difference in the degree of vison loss between control and experimental groups was statistically significant, but the sample size was too small to assume the results would be generalizable to the larger population.

Conclusions: These studies demonstrate that curcumin is beneficial with no significant adverse reactions. The evidence is still inconclusive because of the following limitations; study duration of less than a year, sample populations that were based outside of the US, and small sample size. Future studies should include a more diverse study population and observe the effects of curcumin for a longer period of time.

Key words: "prediabetes", "type 2 diabetes", "curcumin"

INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorders that are characterized by hyperglycemia.[1] Type 2 diabetes mellitus(T2DM) is a metabolic condition in which blood glucose levels in the body stay elevated due to insulin resistance and impaired insulin secretion and utilization.[1] In 2015, Diabetes was the 7th leading cause of death.[2] No single cause of Type 2 diabetes has been identified, but many studies support that insulin resistance is the leading factor, since it precedes the impairment in insulin secretion that ultimately leads to diabetes.[1]

Insulin resistance is the inability of insulin to act on target tissues such as skeletal muscle. It is the predominant feature of T2DM [1] and manifests in patients who are obese and genetically susceptible. Early on, glucose levels and tolerance are normal because the beta cells in the pancreas are able to compensate for the insulin resistance by increasing their insulin output to stimulate glucose-uptake by skeletal muscle. However, as insulin resistance persists, the beta cells can no longer keep up with the demand for insulin, resulting in postprandial hyperglycemia. As insulin secretion declines further, fasting hyperglycemia manifests since there is not enough insulin to suppress gluconeogenesis in the liver. A vicious cycle develops in which this chronic state of hyperglycemia continues to impair beta cell function, prolonging the hyperglycemia.

Visceral obesity in particular[1], and a lack of physical activity are the two most significant environmental factors in the development of T2DM. [3] Obesity is known to decrease beta cell sensitivity to glucose and cause resistance to insulin-mediated glucose uptake.[3]; 12.2% of all adults aged 18 years or older in the US have type 2 diabetes and 87.5% of them were overweight or obese.[2] Weight loss alone can be enough to reverse these effects and normalize glucose levels.[2] Inflammation likely plays a role too; factors released from adipose tissue called adipokines stimulate inflammatory activity which correlates to insulin resistance.[3] Inflammation

is also the likely link between T2DM and atherosclerosis; there are increased levels of inflammatory markers in patients with T2DM such as C-reactive protein, and tumor necrosis factor-alpha. [3] Lifestyle interventions can decrease the levels of these inflammatory markers. [3]

Prediabetes is a term that is used to describe a state of higher than normal blood glucose levels that put patients at risk for developing type 2 diabetes and cardiovascular disease.[4] In the available data from 2015, 33.9% of all adults aged 18 years or older in the US have prediabetes.[2] It is indicated by an A1c of 5.7%-6.4%, a fasting blood glucose level of 100-125 mg/dl, and a 2 hour glucose level of 140-199 mg/dl following the oral glucose tolerance test.[4] Like diabetic patients, they may also be asymptomatic so routine lab studies are crucial in identifying hyperglycemia early on. Identifying pre-diabetic patients is key since they can implement lifestyle changes, such as weight loss, that can lower their risk of developing T2DM.

Management of T2DM is difficult since the degree of insulin resistance and onset of impaired insulin secretion varies from patient to patient.[1] For example, it is not uncommon to start patients on insulin with metformin because many patients may already have long-standing diabetes.[1] Metformin is endorsed by the American Diabetes Association as a low cost, 1st line therapy since it can help promote weight loss and even lower lipid levels.[1] If metformin alone is not enough to reach the blood glucose target of ≤ 200 mg/dL, other agents are added on such as GLP-1 receptor agonists.

Complications related to T2DM not only impose major health consequences, but also comprise a large portion of the financial burden patients face; a type 2 diabetic spends an average of $85,500 over his or her lifetime on doctor visits, medications, and supplies;[5] 53% of this is typically spent on treating complications related to their diabetes.[5] Since many of these are related to inflammation, curcumin is being sought as a natural preventative tool against diabetes

because it is known to be anti-inflammatory with anti-diabetic properties.[6, 7] It is also a low-cost option that is potentially safe for long-term use. [6] Diabetics have 30.3 million healthcare visits a year [8] so physician assistants will undoubtedly encounter these patients in practice and will do a great service to them by offering them remedies that can relieve the burden of their illness.

OBJECTIVE

The objective of this systematic review is to determine whether or not curcumin can manage and prevent major complications for type 2 diabetics or even prevent the onset of type 2 diabetes in pre-diabetics.

METHODS

This systematic review evaluated 3 research studies that fit the inclusion criteria of evaluating adults 18 years of age and older with prediabetes and type 2 diabetes. Any study that dealt with pediatric patients or Type 1 diabetes were excluded. The research articles were found through PubMed and were published in peer-reviewed journals from 2012-2014. Two of the articles were published in English and the third article was originally published in Italian. The articles were found using the key words "prediabetes", "type 2 diabetes", and "turmeric". Two of the studies were double-blinded, randomized controlled studies and the third study was a controlled, therapeutic protocol registry in which subjects were allowed to choose the management protocol they were willing to adhere to for the duration of the study.

The articles were chosen for this review based on their relevance to the clinical objective above and whether they discussed patient oriented evidence that matters (POEMs). Each of the studies assessed how effective curcumin was in delaying the onset of complications related to diabetes and the onset of T2DM itself in pre-diabetics. Of the two double-blinded, randomized

studies, one compared pre-diabetics taking curcumin for 9 months and the other compared

diabetics taking curcumin for 6 months to control groups taking placebo. The therapeutic

protocol registry compared diabetics taking curcumin as an adjunct to their current management

regimen to diabetics who did not add curcumin. ANOVA and p-values were used or reported in

the selected articles.

Table 1-Demographics and characteristics of included studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Chuengsamarn S., 2012 (1)[6]	Double blinded, RCT	240	≥ 35	Pre-diabetics age ≥ 35 who fit one of these three criteria - fasting glucose between 100-124 mg/dL -2hr post-glucose load after oral glucose tolerance test was 140-199 mg/dL -HbA1C was between 5.7-6.4%	-Any subject diagnosed with type 2 diabetes -Any subjects receiving other herbal medicines -Any subjects taking oral hypoglycemic agents.	3	Three 250 mg capsules of Curcuminoid BID x 9 months
Chuengsamarn S., 2014 (2)[7]	Double blinded, RCT	240	≥ 35	Type 2 diabetics age ≥ 35 who fit one of these 3 criteria -fasting glucose was ≥ 126 mg/dL -2hr post-glucose load after oral glucose tolerance test was ≥ 200 mg/dL.	-Pre-diabetics - Anyone receiving other herbal medicines - Anyone taking oral hypoglycemic agents	0	Three 250 mg capsules of Curcuminoid BID x 6 months
Steigerwalt, R., 2012 (3)[9]	Controlled study	77	No age specif ied	Type 2 diabetics -with diabetic retinopathy -BMI of 24-26 -with diabetes for ≥ 5 years -who had been stable for at least 3 months on the standard management protocol of diet, exercise, and oral meds prior to the start of the study.	-Concurrent metabolic disorders -Previous use of insulin -Clinical signs of atherosclero sis -History of diabetic ulcers	0	One 500 mg Meriva tablet (equivalent to 100mg of curcumin) BID x 4 weeks

OUTCOMES

One of the double-blinded studies assessed whether curcumin could delay the progression of prediabetes to diabetes by tallying the number of subjects from the curcumin-treated and placebo-treated groups who were diagnosed with type 2 diabetes mellitus. The other assessed whether curcumin could prevent the onset of obesity by comparing the waist circumference of subjects from the curcumin-treated and placebo-treated groups. The therapeutic protocol registry study assessed whether curcumin could improve visual acuity in patients with diabetic retinopathy by using the Snellen eye chart as a means of comparison.

RESULTS

Both studies by Chuengsamarn et al. from 2012 and 2014 performed data analysis on an intention to treat basis such that those that were lost to follow-up were still included in the analysis of the groups to which they were initially randomized to; however, no data was available about those subjects lost to follow-up. No worse case analysis were performed on the subjects who dropped out.[6,7] The researchers in the study by Steigerwalt et al. did not mention whether their data analysis was done on an intention to treat basis, but they reported that all subjects in the control and experimental groups completed follow-up without any drop-outs. [9] Researchers from all the studies report that all baseline parameters for the control group and the group taking curcumin products were not statistically different.[6,7,9]

In both of the double-blinded studies by Chuengsamarn et al, researchers eliminated confounding variables by educating subjects on the diet and exercise protocols they should follow for 3 months prior to randomization and excluding anyone who was taking other oral medications as mentioned in Table 1. Subjects were instructed to take 3 capsules with blinded

labels of curcumin or placebo twice a day for 6 months[7] or 9 months[6]; the dosages are reported in Table 1. To ensure compliance, researchers had patients bring their capsules to their follow-up visits at 3, 6[6,7] and 9 months[6].

The double-blinded controlled study by Chuengsamarn et al. from 2012 assessed whether or not curcumin could prevent pre-diabetics from developing type 2 diabetes. Out of 240 subjects that were enrolled, 237 subjects were randomized into the curcumin and placebo treated groups with 116 subjects in the control group and 119 subjects in the curcumin group. At the end of their study, no subjects taking curcumin as part of their diet and exercise regimen developed type 2 diabetes, while 16% of the placebo-treated subjects were newly diagnosed with type 2 diabetes.

Since the outcome of developing type 2 diabetes or not was dichotomous data, the treatment effects of curcumin were able to be calculated from this study as reported in table 2 below. These calculations were based on data with a p-value of 0.001 which indicates that the following estimates of the treatment effect are statistically significant.

Table 2: Treatment effects of curcumin from Chuengsamarn et al.[6]

RRR	ARR	NNT
19%	16%	-1/0.16=-7

The RRR demonstrates that pre-diabetic subjects taking curcumin had a 19% lower risk of progressing to type 2 diabetes compared to the subjects taking placebo. The ARR demonstrates that pre-diabetic subjects taking curcumin had a 16% absolute decrease in their risk of developing type 2 diabetes. However, the RRR and ARR values also indicate that the reduction in risk compared to those on placebo wasn't that large since the majority of subjects taking placebo also did not progress to type 2 diabetes. This negative NNT value means that for

every 7 pre-diabetic patients who are given curcumin as a daily supplement for at least 9 months, 1 less pre-diabetic patient will develop type 2 diabetes, compared to the control group. Overall, the difference between the placebo and curcumin treated groups was statistically significant, but the level of risk reduction was not so large.

The 2014 study by Chuengsamarn et al.[7] and the study by Steigerwalt et al.[9] assessed whether curcumin could help reduce the risk of complications in patients with type 2 diabetes. Chuengsamarn et al.[7] evaluated whether curcumin could prevent the onset of abdominal obesity, a major atherogenic risk factor and Stiegerwalt[9] evaluated whether curcumin could reduce the degree of vision loss from diabetic retinopathy. These results were published as ranges, instead of discrete values so they could not be converted to dichotomous data for this review.

Chuengsamarn et al.[7] assessed abdominal obesity by waist circumference which was measured with tape in the horizontal plane midway between the inferior margin of the wrist and the superior border of the iliac crest. While the researchers were able to show that curcumin helped improve the subjects' metabolic profile[7], they found that the decrease in waist circumference in the curcumin treated group from 90.7 to 88.2 cm[7] was not statistically significant as evidenced by a p-value >0.05 for that data. Despite the reductions in waist circumference and abdominal obesity in the subjects taking curcumin, the authors acknowledged that they could not prove whether this reduced their risk of atherosclerosis. However, it is noteworthy that none of the subjects in the placebo-treated group had a decrease in their baseline waist circumference.[7]

The study by Steigerwalt et al[9] sought to determine whether curcumin could help reduce the degree of vision loss in patients with diabetic retinopathy, a major cause of blindness in this population. [9] They tested a product called Meriva, which is curcumin complexed with

phosphatidylcholine that is known to have better bioavailability than the natural product. [9,10] Researchers eliminated confounding variables by only accepting diabetics who did not have any atherosclerotic disease; the rest of the inclusion criteria is listed in Table 1.

In this study, subjects were offered 2 management plans and they were able to choose which they would like to follow for the duration of the study. The control group of 39 subjects agreed to follow the standard management plan of diet, exercise, and oral medications, while the experimental group of 38 subjects added Meriva to the standard management plan for 4 weeks. Subjects were instructed to take a 500mg Meriva tablet twice a day before meals, corresponding to a daily dose of 200mg of curcumin.[9]

At the end of the 4 week study, subjects taking Meriva had improved visual acuity as evidenced by changes in the Snellen eye scale. Both groups initially had moderate vision loss defined as a score of 20/80-20/160.[9] The group taking Meriva were the only subjects whose visual acuity improved to a score of 20/32-20/78, which reflects mild vision loss.[9] Visual acuity in the control group improved, but their scores were still within the range of moderate vision loss. The researchers report that they used ANOVA to evaluate their before and after results, but they did not publish their test statistic, F. Regardless, these results were statistically significant as evidenced by a p-value of <0.025 for that data.[9]

The 2012 and 2014 studies by Chuengsamarn et al.[6,7] concluded that curcumin could be safely used by patients for at least 9 months without serious adverse effect based on their findings that only 2 subjects had constipation, 1 subject had vertigo, and another had nausea.[6,7] The researchers mention that their results are reliable because there were no issues of compliance between the placebo and curcumin treated groups since the number of capsules subjects in both groups had remaining at each follow-up visit were similar.[6,7]

Table 3: Summary of the statistical significance of the outcomes in the included studies

Chuengsamarn et al, 2012	Chuengsamarn et al, 2014	Steigerwalt et al, 2012
p<0.001	p>0.05	p<0.025

DISCUSSION

This systematic review found that curcumin certainly had a beneficial effect on subjects, but, not all of the results demonstrated a significant difference between subjects taking curcumin from those who did not. Furthermore, despite the researchers' efforts to avoid confounding variables, the results from these studies are not generalizable since the subjects did not hail from the US and these studies did not use the same curcumin product. None of the studies ran for even a year, so it is difficult to conclude that the effects of curcumin were long-lasting.

In both studies by Chuengsamarn et al[6,7], the researchers tried to keep all subjects on the same routine for exercise and diet to limit variability with daily reminders by nutritionists so this helps to make the results generalizable to some extent. However, the subjects were all residents of a small province in central Thailand so it is uncertain whether subjects in the US who hail from different racial backgrounds and ethnicities will experience the same metabolic effects. Steigerwalt et al[9] did not report any patient characteristics, such as the ethnicity or geographical region they hailed from, which makes it difficult to assess the generalizability of their results.

In these studies, subjects were followed for less than a year so it is uncertain how sustainable the effects of curcumin are. For example, despite the results in Chuengsamarn et al[7] that no pre-diabetic taking curcumin developed type 2 diabetes, there is still a possibility of developing type 2 diabetes in the long-term despite taking curcumin.[7] Even though Steigerwalt,

et al boast that their study design optimizes compliance since their subjects chose the protocol they were willing to follow[9], the duration of their study was only 4 weeks so it is unknown whether the subjects would adhere to the regimen long-term. In addition, their study was not double-blinded since the subjects were able to choose which protocol they wanted to follow and the researchers knew which subjects chose what protocol. Thus, there is a high risk of bias here since the subjects knew that they were in the experimental group and this could have influenced their behavior during the study.

The results from this systematic review are also not generalizable because Steigerwalt et al tested a type of curcumin that is not the same as the natural product. Meriva is a lecithin delivery system of curcumin that offers better bioavailability because it is complexed with a phospholipid, phosphatidylcholine, which helps to fixate the otherwise polar curcumin within the inner lipid compartment of the cell membrane.[10] This helps to increase its plasma bioavailability since phospholipids are easily exchanged between cell membranes and extracellular fluid.[10] The degree to which vision improved in subjects taking Meriva compared to subjects who did not add it to their routine was statistically significant, but it is unknown whether diabetics taking natural curcumin would experience the same degree of improvement in their retinopathy. Furthermore, the sample size of only 77 participants was too small for the results to be representative of the larger diabetic population and may have overestimated the treatment effect.

Turmeric has been used medicinally for centuries in Hindu medicine for its anti-inflammatory and antioxidant effects.[11] This makes it invaluable in the management of chronic inflammatory states, such as type 2 diabetes, that make patients prone to developing obesity, atherosclerosis and microvascular disease, such as diabetic retinopathy.[7,9] It is generally available in the US in capsule form and most manufacturers instruct buyers to take 1-3 500mg

capsules daily with or without food. Curcumin is the active compound of turmeric that is often studied in clinical trials.[11] Few adverse reactions have been reported with turmeric in the US, even at high dosages.[11] Most of the reported side effects have been GI-related with rare cases of anaphylaxis.[11] Turmeric has a high concentration of oxalate so it may increase the risk of kidney stones in those who are susceptible, but there have been no reports of this thus far. [11]

CONCLUSION

Based on this review, the evidence is still inconclusive as to whether or not curcumin can manage and prevent major complications for type 2 diabetics or even prevent the onset of type 2 diabetes in pre-diabetics. The outcomes are promising, but the results were based on a time-frame of less than a year so it cannot be assumed that the outcomes were sustainable long-term.

Future studies on curcumin should be done on a larger nationwide scale where US residents from all states with various demographics would be included. One limitation with these studies is that their results are based on subjects who were all from the same ethnicity and living in the same region. More research must be done to assess whether curcumin would have a beneficial effect on people of different ethnicities and whether each ethnic group would experience a benefit to the same degree. Cohort studies of pre-diabetics and diabetics taking curcumin with their daily regimen can be useful for assessing whether patients can tolerate long-term daily intake without significant adverse reactions and whether the effects of curcumin are sustained long-term with daily intake.

Overall, this review demonstrates that curcumin can have a positive impact on diabetics as a lifestyle intervention. It may help reduce visceral obesity, which will decrease their risk of cardiovascular and inflammatory complications and improve their quality of life.

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