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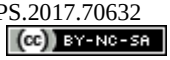
ISSN 2231-3354 

Mechanisms and biological effects of Caffeine on substrate metabolism homeostasis: A systematic review

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ABSTRACT

Objective: This review aims to elucidate the possible effects of caffeine over homeostasis mechanism of energetic subtracts metabolism.

Methods: The study was carried out in systematic review form and its sample comprised six scientific papers published in academic journals. Only the studies involving soccer players (professionals and amateurs, except goalkeepers) were included in this review.

Results: Caffeine was able to increase insulin and serum glycemia levels, after oral glucose tolerance test (OGTT), demonstrating that caffeine alters blood glucose maintenance in diabetic men. A decrease of insulin sensibility evaluated by insulin sensibility index (ISI) rates was observed. Also showed that the administration of caffeine was able to control the catecholamine levels. Nevertheless, demonstrated that long-term consumption of caffeine may be efficient in controlling glucose and adiponectin levels, which would be good for the prevention as well as for the associated complication of diabetes mellitus.

Conclusion: Caffeine is one of the active compounds of coffee and its consumption is being suggested as benefic over glucose tolerance. Albeit, acute and chronic studies are demonstrating controversial results, showing differences in blood glucose levels, such as enhancement, reduction and also, no changes, after the consumption of different doses of caffeine. The mechanism to explain this events is yet unknown, however it is suggested that caffeine may act over insulin clearance. Some studies are aiming to evaluate the action of caffeine over insulin sensibility. Caffeine may act reducing insulin sensibility over its receptors.

Abbreviations
OGTT: Oral Glucose tolerance test; ITT: Insulin Tolerance Test; ISI: insulin sensibility index; ORAC: oxygen radical absorbance capacity; NF-kB: nuclear factor kappa B; FFA: free fatty acids; NEFA: non-esterified fatty acids; AMPK: 5′-AMP activated protein kinase; IGF: insulin growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor.

INTRODUCTION

Diabetes mellitus type 2 (DMT2) is a chronic disease associated with high rates of morbidity, followed by long term complications and premature mortality (Nathan, 1993; WHO, 2016). Coffee is the most consumed beverage in the world and its consumption is being associated with lower risk of diabetes, but a few is known about the mechanisms responsible to this association (van Dam and Hu, 2005; van Dam *et al*., 2006; Sartorelli *et al*., 2010). Caffeine is one of coffee's active component and its beneficial effects over glucose tolerance are being deeply investigated (van Dam *et al*., 2006; Sartorelli *et al*., 2010). Controversial results were found in acute and chronic studies using caffeine, reporting differences in blood glucose levels

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such as an enhancement (Robinson *et al*., 2004; Battram *et al*., 2006; Moisey *et al*., 2008), reduction (Urzúa *et al*., 2012; Conde *et al*., 2012; Guarino *et al*., 2013) or no changes (Urzúa *et al*., 2012; Conde *et al*., 2012; Guarino *et al*., 2013) after the consumption of different doses of caffeine.

Caffeine mechanism of action

Adenosine is an important component of purinergic system, and it is found in all tissues presenting a modulatory role in several physiological processes (Fredholm *et al*., 1999). Adenosine acts through four subtypes of receptors, however, A_1 and A_3 receptors found in the skeletal muscle, adipose, and liver cells, may be connect to G protein, inhibiting the activity of the enzyme adenylyl cyclase. This inhibition activate the G protein which, suppress the conversion of ATP to cAMP, decreasing the levels of second messenger, not activating protein kinase A (PKA) that act to stimulate skeletal muscle, adipose, and liver cells (Raney and Turcotte., 2008).

Methylxanthine, as caffeine, are competitive antagonists, not selective of adenosine receptors (Conde *et al*., 2012). Caffeine is more potent to A_{2A} receptors and less potent to A_3 receptors (Fredholm *et al*., 1999). The action of caffeine over A_{2A} receptors increases the concentration of intracellular cAMP, triggering several responses, such as metabolic (lipolysis and glycogenolysis in muscle; glycogenesis in liver), cardiovascular (vasoconstriction) and neuronal (glutamate release) (Fredholm *et al*., 1999).

In addition, caffeine stimulates through the action over adenosine receptors, Ca^{2+} release in sarcoplasmic reticulum (SR), acting by the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which is involved in other cascades of enzymatic activation in the cell (Rose e Richter, 2005; Canto *et al*., 2006).

Caffeine is being shown to be related with the regulation of glucose and lipid metabolism in skeletal muscle. Studies observed that caffeine may increase the concentration of different glucose carriers (GLUT), such as GLUT2 and GLUT4 (Canto *et al*., 2006; Wright *et al*., 2005; Park *et al*., 2009). Caffeine stimulates the insulin-independent glucose carrier (Wright *et al*. 2004; Jensen *et al*. 2007) and enhances the expression of RNAm of GLUT4 and fatty acids metabolism (Mukwevho *et al*., 2008), presenting metabolic effects similar to 5′-AMP activated protein kinase (AMPK). AMPK is a metabolic sensor which has an important role in lipid metabolism regulation, as well as in glucose homeostasis. By the simultaneous inhibition of lipogenesis and lipolysis in adipose tissue, the activation of AMPK decreases the stratified lipid circulation and fat deposition (Long and Zierath 2006); increases lipid oxidation in liver and muscle (Luo *et al*., 2005; Ruderman and Saha 2006), contributing to an improvement in insulin sensibility in the organism. AMPK reduces liver glucose production and enhances glucose capture in skeletal muscle, presenting an important role in glucose homeostasis. It is being demonstrated that caffeine increases GLUT4 mRNA and insulin independent carriers in skeletal muscle through processes mediated by AMPK (Egawa *et al*., 2009). The Ca^{2+} released by SR is a prerequisite to muscle contraction, and may be a sign to the muscle to capture more blood glucose (Rose and Richter, 2005; Canto *et al*., 2006). Two parallel pathways of glucose uptake stimulation, AMPK or CaMKII are necessary and sufficient to maintain muscular glucose input, in order to obtain enough energy to muscular contraction (Wright *et al*., 2004; Wright *et al*., 2005 Raney and Turcotte., 2008). Caffeine may stimulate Ca^{2+} release of SR (Canto *et al*., 2006, Wright *et al*., 2004; Wright *et al*., 2005), increasing the phosphorylation of AMPK and activating CaMKII, enhancing the translocation of GLUT4, triggering a greater glucose uptake.

Beyond glucose, fatty acids are important to the maintenance of cellular energy. The liberation of Ca^{2+} by SR in physical stimulus result in an enhancement of fatty acid harvesting, through the increase of AMPK phosphorylation and a consequent increase of kinase proteins regulated by extracellular sign 1 and 2 (ERK1/2), activated by CaMKII (Rose and Hargreaves, 2003; Wright *et al*., 2005). Caffeine affects the glucose harvesting (Wright *et al*., 2004) by intracellular Ca^{2+} increase and activation of AMPK, however, the fatty acids harvesting could be evolved through the increase of ERK1/2 action becoming a parallel metabolic pathway.

Thus, the description of caffeine effect over glucose and fatty acids harvesting and oxidation in skeletal muscle tissue, as well as the mobilization of adipose tissue already mentioned, demonstrate the complex maintenance pathway of the body metabolic homeostasis (Figure 1).

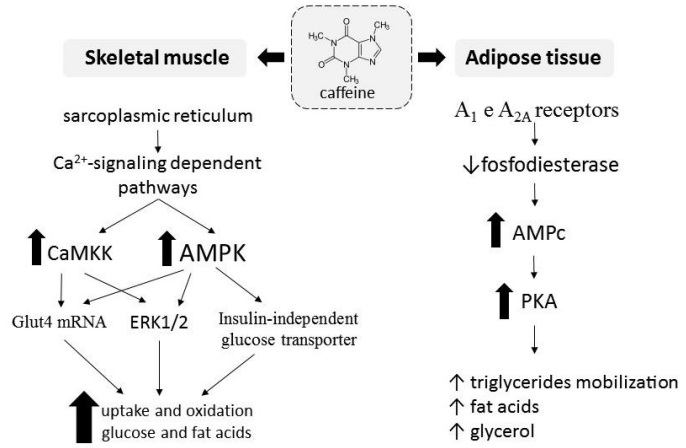

Fig. 1: Possible mechanism of fatty acid and glucose harvesting in skeletal muscle cell and in adipocyte by caffeine.

The relation between caffeine and diabetes, reported by the letter of Kerr and Evert (2005), and demonstrated in initial studies (van Dam *et al*., 2004, Yamaji *et al*., 2004), is that the consumption of coffee reduces the risk of developing DMT2. The mechanisms are yet unknown, but it is suggested that it can act over insulin release and action. Some studies are aiming to evaluate the action of caffeine over insulin sensibility, and this effect could be of reducing the sensitivity of insulin over its receptors. Therefore, this review aims to elucidate possible effects

of caffeine over homeostasis mechanism of energetic subtracts metabolism.

Methods

This systematic review of literature was conducted in the period of November 2015 and October 2016 utilizing databases such as PubMed, Lilacs, Scielo, Bireme, Google Scholar and Science Direct. In order to obtain the studies, the following key-words were utilized: "Diabetes mellitus", "Metabolism and Caffeine", "Caffeine and Glucose", "Caffeine and Diabetes", "Caffeine and insulin sensibility", "Caffeine and insulin secretion" and "Caffeine, Diabetes and glucose uptake". Furthermore, studies that were cited in the selected articles were verified.

Studies on association of caffeine, diabetes and exercise were included. Those excluded were: a) association between exercise and diabetes only; b) association between caffeine and diabetes only; c) association between exercise and caffeine only; d) studies that utilized other isolated or concomitant supplementation.

RESULTS

From the researches made in the mentioned databases, there were 654 articles related to the key-words, from which, based on the titles scanning, 88 studies were separated in order to read the respective abstracts. After reading, 39 articles were selected to a complete reading and from these, 13 studies matched with the inclusion criteria and then were selected to this review.

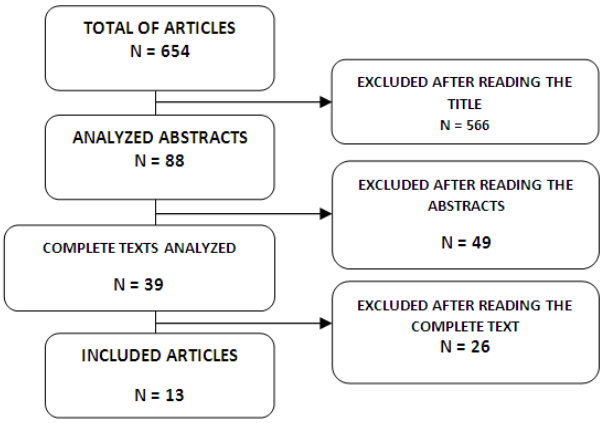

Fig. 2: Organogram of the stages to sample delimitation.

In table 1 there are twelve articles in which caffeine intake analysis in situation of metabolic assessment, with pre-clinical models (animals) and clinical ones (humans).

Table 1: Baseline characteristics of articles which reported effects of caffeine on homeostasis mechanism of energetic subtracts metabolism.

Author	Dose of caffeine	Diabetes mellitus models	Assessment	Biological effects
Battram *et al*. (2006)	4,5 mg/kg	Healthy men	OGTT	↑ insulin and peptide C; ↑ glycemia (50%) 90 min ↑ glycerol ↑ epinephrine
Bhaktha *et al*. (2015)	N/E	220 Healthy men and 48 man with DMT2	Blood analyses (5 mL) in fasting	↓ glycemia (11%) ↑ adiponectin (20%) ↓ HbA1c (4,5%)
Chu *et al*. (2011)	N/E	Human cells *in vitro*	Hepatocytes with carcinoma HEPG2 and adipose cells	↓ ORAC ↓ NF-kB ↑ glucose uptake (??)
Conde *et al* (2012)	6,78 mg/kg	Wistar rats with high fat and dextrose diet	ITT	↓glycemia (19%) ↓ insulin (10%) ↑ insulin sensibility (45%) ↓ FFA (35%) ↓ catecholamine (124%)
Egawa *et al* (2009)	3 mmol/L	97 male Sprague-Dawley rats	Rat *epitrochlearis* and soleus muscles	↑ AMPK (40%) ↑ Acetyl-CoA carboxylase (50%) ↑ 3-O-methyl-D- glucose carrier (20%)
Guararino *et al*., (2013)	25 mg/kg	24 months aged wistar rats	ITT and gene expression	↑ insulin sensibility (40%) NEFA (NC) Epinephrine (NC) ↑ AMPK (60%) ↑ Glut4 (50%)
Moisey *et al* (2008)	5 mg/kg	8 healthy men	OGTT	↑ insulin (29%) ↑ peptide C (40%) ↑ blood glucose (147%)
Park *et al* (2007)	35 mg	Sprague-Dawley diabetic pancreatectomized rats	Hyperglycemic clamp during OGTT	↑ insulin sensibility (25%) ↑ glucokinase (50%) ↑ hyperplasia cell β (21%) ↑ IGF (25%)

Petrie *et al* (2004)	5 mg/kg	9 obese men	OGTT	↑ Insulin (36%) ↑ peptide C (35%) ↑ FFA (60%) ↓ ISI (25%)
Robinson *et al*., (2004)	5 mg/kg	Obese men with DMT2	OGTT	↑insulin (25%) ↑ peptide C (26%) ↑glycemia (25%) ↓ ISI (14%)
Urzua *et al*., (2012)	93 mg/kg	Streptozotocin-induced diabetes mellitus rats	OGTT	↓glycemia (19%)
Wedick *et al*., (2011)	N/E	45 man over weight (BMI = 25-30 kg/m^2)	ISI, OGTT	insulin sensibility (NC) glucose tolerance (NC) insulin secretion (NC)
Yamauchi *et al*., (2010)	290 mg/L	Mice spontaneously diabetic (KK-Ay	ITT and gene expression	↓glycemia (30%) ↑ insulin sensibility (50%) ↓ IL-6 (40%) ↓ TNF-a (30%)

N/E: Not evaluated; NA: No alterations; OGTT: Oral Glucose tolerance test; ITT: Insulin Tolerance Test; ISI: insulin sensibility index; ORAC: oxygen radical absorbance capacity; NF-kB: factor nuclear kappa B; FFA: free fatty acids; NEFA: non-esterified fatty acids; AMPK: 5′-AMP activated protein kinase; IGF: insulin growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor.

Insulin sensibility and glucose tolerance assessment after caffeine consumption

Battram *et al* (2006) investigate the acute (4,5 mg/kg) and chronic (two weeks) effect of caffeine in healthy men (23± 0.6 years, 74 ± 1.9 kg) over glucose and insulin homeostasis. The results of OGTT (Oral Glucose tolerance test) suggest an increase in insulin and peptide C concentrations after the consumption of caffeine, where compared to placebo group and decaffeinated one. However, the glucose levels after 90 minutes of test were 50% higher compared to place and decaffeinated groups. After 12 min. though, a glycemic control occurred, with no difference between groups. The glycerol concentration increases during caffeine consumption (126 to 154 umol/L) after 60 min, compared to other groups, as well as epinephrine concentration, which increased in the caffeine groups in 60, 90 and 120 min. compared to control groups. Robinson *et al*., (2004) evaluate obese men with DMT2. Caffeine was able to increase insulin (25%) and serum glycemia (25%) levels, after OGTT, demonstrating that caffeine alters blood glucose maintenance in diabetic men. Moisey *et al* (2008) demonstrated in their study with healthy men, that the consumption of caffeine (5 mg/kg) before OGTT increase blood glucose (147%), insulin (29%) and peptide C (40%) compared to the values of decaffeinated control group after 60 min.

Petrie *et al* (2004) assessed the effect of caffeine (5 mg/kg) over glucose and insulin homeostasis in obese men. After OGTT caffeine increased 36% the concentration of serum insulin without altering the values of blood glucose, however, with a decrease of insulin sensibility evaluated by insulin sensibility index (ISI) rates. In a study with diabetic rats Urzua *et al* (2012) gave 93 mg/kg of caffeine daily (the same of 3 cups of coffee) for 60 days. In nondiabetic animals, caffeine did not trigger any difference in blood glucose levels, however, in both groups the OGGT was favorable. Conde *et al*. (2012) evaluated the long-temp (15 days) caffeine consumption (6.78 mg/kg) in healthy rats and rats that received a fat diet. Caffeine revert insulin resistance condition of the animals which received the fat diet, restoring plasmatic insulin levels and controlling glucose and free fatty acid levels. This study also showed that the administration of caffeine was able to control the catecholamine levels (adrenaline and noradrenaline) in this group, reducing them up to 124% when comparing to the values of pre-consumption and further decreased sympathetic nervous system stimulation. Wedick *et al*. (2011) evaluated the effect of the consumption of 5 cups of coffee (caffeinated and decaffeinated) for 8 weeks, over DMT2 risk factors, in 45 men over weighed. No alteration was observed in the following parameters: ISI, oral glucose tolerance test (OGTT) and insulin secretion. In a study made by Guarino *et al*. (2013), it was demonstrated that chronic caffeine consumption (25 mg/kg) controlled glucose and fatty acids levels and reverted insulin resistance condition induced by aging in wistar rats. These effects were measured by the increase of AMPK activity and translocation of GLUT4. Bhaktha *et al*. (2015), demonstrated that long-term consumption of caffeine may be efficient in controlling glucose and adiponectin levels, which would be good for the prevention as well as for the associated complication of diabetes mellitus.

Some studies demonstrated metabolic mechanism after caffeine administration. Park *et al*. (2007) investigated the effect and mechanisms of caffeine (30 mg) and sucrose (21g) over glycemic metabolism of pancreatectomized Sprague-Dawley diabetic rats. After 12 weeks of caffeine administration, the animals exhibited an increase in insulin sensibility, without any alteration in glucose levels, and an increase of glucose-stimulated insulin, and also occurring hyperplasia of β cells. An insulinotropic effect was observed, which may be explained by signalization cascade of insulin-1 growth factor (IGF-1) and increase in glucokinase activity. Besides that, sucrose consumption worsened insulin sensibility and attenuated the IGF-1 signalization in pancreatic islets. These findings indicate that long-term consumption of caffeine, further than altering the glycemic metabolism, also increased insulin sensibility and beta cells function in diabetic animals. Egawa *et al*. (2009) evaluate the effect of caffeine (3 mmol/L) over glucose capitation evolved in

the metabolism regulation, in epitrochlearis cells and soleus muscles of rats, *in vitro*. Caffeine increased the phosphorylation of AMPK and acetyl coenzyme A carboxylase, associated with the reduction of phosphocreatine. An increase in glucose transportation rate was also demonstrated, by the activation of 3-O-methyl-D glucose carrier, which is not stimulated by insulin. These results suggest that the effect of caffeine is similar to the physical exercise, improving and increasing glucose capitation through the activation of AMPK and glucose carriers that are not associated to insulin.

Yamauchi *et al*. (2010) evaluated the antidiabetic effect of coffee and caffeine consumption in spontaneously diabetic mice (KK-Ay). Coffee intake improved the hyperglycemic condition (2 fold), increased insulin sensibility and reduced inflammatory factors (IL-6 and TNF-α). Caffeine consumption (290 mg/L) also improved the hyperglycemic condition and enhanced insulin sensibility. Chu *et al*. (2011) conducted a study to evaluate the action of bioactive compounds of coffee over antioxidant, inflammatory factors (inhibition of NF-Kb and TNF-α) and the stimulation of glucose capitation *in vitro*. Bioactive compounds of coffee (phenolic compounds and caffeine) demonstrated a cellular antioxidant action in oxygen radical absorbance capacity (ORAC) test in hepatocytes with human HEPG2 carcinoma, as well as the capability of reducing NF-Kb activation and increase glucose capitation in human adipose cells.

Caffeine biological effect in the organism

Regarding to fasting and postprandial glycemic values, caffeine consumption reverts and controls hyperglycemic levels typical of the diabetic condition, and also controls the plasmatic insulin levels. Caffeine administered before the oral glucose tolerance test (OGTT) in doses between 4.5 and 93 mg/kg did not alter glycemic and insulin values after 30 min. However, after 60 and 90 minutes, caffeine tend to maintain glycemic and insulin levels high, comparing to groups without caffeine. This occurs to healthy, obese with glucose intolerance, diabetic men and also to diabetic rats or rats that received fat diets. Nonetheless, after 120 min, no difference was observed in glucose and plasmatic insulin concentrations.

Caffeine may alter insulin sensibility and glucose tolerance during OGTT, at short term. The studies demonstrated that caffeine consumption reduced the insulin sensibility by ISI rates, but modified glucose tolerance condition during OGTT. Insulin action reduction and glucose capture increase may be the key to explaining this enigma. Mechanisms that are insulin-independent (AMPK, 3-O-methyl-D-glucose carrier, glucokinase and GLUT2) may be sensitized during the action of caffeine triggering a better glucose tolerance and interaction of caffeine molecule over adenosine receptors.

The increase of CNS activity is associated with the increase of catecholamine circulation that trigger insulin resistance (Seals and Bell, 2004), which triggers an increase of lipolysis in adipose tissue, enhancing non-esterified fatty acids (NEFA) levels (Lafontan and Langin, 2009), increasing gluconeogenesis and glycogenesis stimulus, contributing to the hepatic glucose production (Exton and Park 1968; Exton *et al*., 1972). The endogenous increase of glucose associated with glucose capitation decrease in skeletal muscle and the oxidation of fatty acids (Young *et al*., 1985; Acheson *et al*., 2004; Mulder *et al*. 2005) cause hyperglycemia.

On long-term, studies demonstrated that caffeine did not alter (Wedick *et al*., 2011) or increased glucose tolerance (Guarino *et al*., 2013) and insulin sensibility (Yamauchi *et al*., 2010).

Other caffeine interaction reflects over glycerol plasmatic levels during OGTT, which is maintained elevated after the administration of the substance. The increase of fatty acids and glycerol with the action of caffeine over adenosine receptors enhances AMPc levels and fostering fatty acid mobilization. Battram *et al*. (2006) demonstrated an increase in catecholamine, fatty acid and plasmatic glucose levels during OGTT to the group of healthy men that received caffeine acutely, however, Conde *et al* (2012) demonstrated in rats with glucose tolerance that chronic consumption of caffeine (15 days) reduced the levels of catecholamines, fatty acids and plasmatic glucose.

In hyperglycemic conditions, the increase of insulin and triglycerides synthesis are stimulated, being opposed action ways. The main point about the influence of caffeine in glucose, insulin, fatty acids and glycerol levels during the metabolic state is curious, because this increase is contradictory to the liberation and synthesis of these substrates. This phenomenon may be explained by the upregulation of AMPK, effect of Ca^{2+} intracellular input triggered by caffeine (Jensen *et al*., 2007), which increased the action of the enzyme activated in GLUT4, CaMKII and ERK1/2, conduction a higher glucose and fatty acids capitation to the cells. Nonetheless, few studies aimed to elucidate the action of caffeine over the predominance of substrates and their entrance to cellular oxidation.

Future directions

Regarding to the evaluation of glycemic and fatty acids control, it is important to have consensus based on the best type of evaluation to verify the homeostasis of the energetic substrates metabolism, as well as on the evolvement of caffeine over the control, maintenance, consumption and synthesis of these substrates.

The condition of glucose tolerance becomes better with the consumption of caffeine in some studies, however, in others, this condition is worsened. There is a need of clarification regarding to the accuracy of the evolvement of this drug over the consumption and oxidation of energetic substrates related to cellular metabolism.

Insulin sensibility is perhaps a paradox when the effects of caffeine appear. This mechanisms and consequent alterations triggered by caffeine in the metabolism, in order to understand its pharmacology and its possible benefits and harms.

There is a need for studies that demonstrate the action of caffeine over: the glycemic and fatty acids behavior fo the alteration of catecholamine levels, insulin sensibility, glucose

tolerance in humans. Studies aiming to evaluate the mechanism and effects of caffeine in the homeostasis of energetic metabolism may contribute to the combat against condition such as glucose intolerance, insulin resistance and diabetes mellitus.

CONCLUSION

The divergences of caffeine effects may give us a clue to find how it operates in the organism, due to the biological actions of this molecule over different tissues. This may an antagonist role such as glycogenic (hepatocytes) and glycolytic (skeletal muscle and adipose tissue) conditions, corresponding to adenosine receptors and Ca^{2+} intracellular concentrations, which influence the presence of enzymes that regulate metabolic substrates.

Furthermore, long-term consumption of caffeine seems to be more efficient in controlling glucose and adiponectin levels, which would be beneficial to the prevention as well as to the complication that are inherent to diabetes mellitus. Thus, with different action pathways, and with recent studies reporting favorable condition in the glycemic control in diabetes condition, caffeine may help controlling this disease that plague the world.

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