Selected 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors. A look into their use and potential in pre-diabetes and type 2 diabetes

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Objectives. This review assesses the comparative safety and efficacy of selected 3-hydroxy-3-methylglutaric acid coenzyme A inhibitors (statins, cinnamic acids, 3-hydroxy-3-methyl glutaric acid) on the pre-onset type 2 diabetes (PT2D) and post-onset type 2 diabetes (T2D)-related cluster of seven features (central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation).

Methods. Google scholar and PubMed were searched for statin*, flaxseed lignan complex (FLC), cinnamic acid (CA)*, and 3-hydroxy-3-methylglutaric acid (HMGA) in conjunction with each of PT2D, T2D and the cluster of seven. An introduction was followed by findings or absence thereof on the impacts of each of statins, FLC, CAs and HMGA on each member of the cluster of seven.

Results. Pravastatin manages three features in PT2D, while a number of the statins improve five in T2D. FLC is negative in PT2D but controls four in T2D; it is not clear if the CAs and HMGA in FLC play a role in this success. CAs have potential in six and HMGA has potential in three of the cluster of seven though yet CAs and HMGA are untested in PT2D and T2D in humans. There are safety concerns with some statins and HMGA but FLC and CAs appear safe in the doses and durations tested.

Conclusions. Selected statins, FLC, CAs and HMGA can manage or have a potential to manage at least three features of the cluster of seven. Most of the literature-stated concerns are with select statins but there are concerns (one actual and two potential) with HMGA.

Key words: statins, flaxseed lignan complex, cinnamic acids, 3-hydroxy-3-methylglutaric acid, 3-hydroxy-3-methylglutaric acid coenzyme A reductase inhibition, type 2 diabetes mellitus, central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation

A cluster of seven features (central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation) in whole or in part is associated with pre-type 2 diabetes (PT2D) or type 2 diabetes (T2D). Each member of the cluster contributes to atherosclerosis and its sequelae, myocardial infarction and stroke, the two major causes of death in T2D patients (Sasaki et al. 1995; Alberti et al. 2007; Sharma et al. 2017). This paper was prompted by findings that 3-hydroxy-3-methylglutarate coenzyme A reductase inhibitors (HMG-

CoA RIs) (statins; cinnamic acids, CAs; 3-hydroxy-3-methyl-glutaric acid, HMGA) (Di Padova et al. 1982; Istvan and Deisenhofer 2001; Lee et al. 2007; Prabhakar and Doble 2011; Sirtori 2014) have the ability or potential ability to manage a number of members of the cluster of seven as does flaxseed lignan complex (FLC) (Peterson et al. 2010; Prasad et al. 2020) containing CAs and HMGA (Muir 2006). FLC also contains secoisolariciresinol diglucoside (SDG), but there is no evidence that it or its mammalian derived lignans, enterodiol and enterolactone, are HMG-CoA

RIs and so their effects (Barre and Mizier-Barre 2020) are not mediated by HMG-CoA R inhibition. Consequently, the focus of this paper will be on FLC, CAs and HMGA compared to statins, the most commonly prescribed HMG-CoA RIs.

Central obesity

Central obesity is a frequent pre-cursor of PT2D and T2D. There are no reports indicating that any of the statins reduces or manages central obesity. Atorvastatin dose (20 vs. 40 mg/day) (Maksymets et al. 2019) does not decrease waist circumference in obese non-diabetic patients. However, FLC (600 mg SDG/day) (Barre et al. 2012) very modestly decreased waist circumference gain over a three-month period in older T2D patients. What if anything CA and/or HMGA in FLC had to do with the modest decrease in waist circumference gain is not clear. There are no reports CAs or HMGA managing central obesity in PT2D or T2D but in high fat diet induced-obese rats, CA caused reduced weight gain (Mnafgui et al. 2015). Yousufzai and Siddiqi (1977) found that HMGA reduced triglyceride in epididymal fat and caused less weight gain in rats fed an atherogenic diet. While it appears that there is nothing published on CAs and HMGA central adiposity management in humans, it would be of interest to see the results of such investigations.

Hyperglycemia

Pravastatin increased insulin sensitivity, lowered fasting plasma glucose and HbA1c after 10 weeks on 20 mg q.d. at bedtime in those with metabolic syndrome, and hence it was hypothesized that Pravastatin may manage metabolic syndrome so as to reduce their risk of T2D (Guclu et al. 2004; Yamagishi et al. 2006). However, Maksymets et al. (2019) showed higher insulin resistance and fasting plasma glucose at 40 vs. 20 mg/day Atorvastatin in obese non-diabetic persons. Similarly, Jula et al. (2002) suggested the possibility of heightened insulin resistance with Simvastatin in hypercholesterolemic non-diabetic men. Thus, dose and structure-function relationships are consistent with the poorer glycemic control in T2D patients on Atorvastatin but not Pitavastatin and Pravastatin (Yamakawa et al. 2008). Pitavastatin improves glycemic control in T2D patients (Cui et al. 2018). Cornish et al. (2009) observed no change in fasting serum glucose as the result of FLC consumption in non-diabetic persons with metabolic syndrome. Barre et al. (2012) noted an FLC

induced decrease in fasting plasma glucose in older T2D patients. It must be pointed out that the plasma glucose decrease described by Barre et al. (2012) is not necessarily due to HMG-CoA R inhibition via CAs and/or HMGA as FLC also contains SDG, albeit not an HMG-CoA RI; as well other CA- or HMGA-induced mechanisms may be at play. For example, HMG-CoA expression is reduced by CA in differentiated 3T3-L1 adipocytes and CA improves 2-deoxyglucose uptake into those cells (Prabhakar and Doble 2011). Whether CA caused improved 2-deoxyglucose uptake via reduced HMG-CoA expression is not clear. As well, CA lowered hepatic HMG-CoA activity in high cholesterol fed healthy rats (Lee et al. 2007) but no reference was made in that paper to glucose, and it is not clear from the literature if hyperglycemia management can result from HMG-CoA R inhibition. CA decreased fasting blood glucose in db/db T2D model mice (Yoo et al. 2012) and in non-obese T2D rats (Cicero and Colletti 2016), decreased serum glucose in alloxan-induced T2D rats (Wang et al. 2015) and improved glucose tolerance *in vivo* in streptozotocin-induced T2D rats (Hafizur et al. 2015). HMGA lowered fasting plasma glucose in healthy male mice (Witherup et al. 1995). Interestingly, HMGA aciduria (Hammond and Wilckhen 1984) and HMG-CoA lyase deficiency (Douillard et al. 2012) are associated with hypoglycemia in humans (Wysocki et al. 1976; Duran et al. 1978); HMGA aciduria is caused by HMG-CoA lyase deficiency (Fernandes et al. 2016) and HMGA inhibits HMG-CoA lyase (Witherup et al. 1995). An HMGA containing flavonoid glucoside chamaemeloside improved glucose tolerance and fasting plasma glucose in healthy mice perhaps due to the HMGA moiety release *in vivo* from the chamaemeloside causing HMG CoA lyase inhibition and making the chamaemeloside a prodrug (Konig et al. 1998). König et al. (1998) speculated that the improved fasting plasma glucose could have been due to lowered gluconeogenesis with improved glucose tolerance arising from decreased intestinal glucose absorption and increased hepatic and peripheral glucose disposal but the role, if any, of HMGA on those factors is not clear from that paper.

Hypertension

Guclu et al. (2004) demonstrated a drop in both systolic and diastolic pressures in female metabolic syndrome patients taking Pravastatin (20 mg/day, 10 weeks), suggesting that meant a lower risk for T2D development; however, the mean pre-treatment diastolic pressure was not hypertensive. Maksymets

et al. (2019) reported that obese but non-diabetic patients did not have lower systolic and diastolic pressures on 40 vs. 20 mg/day Atorvastatin but a greater percentage of those on the higher dose fell below the 140/90 target. On a speculative note, Atorvastatin thus may have contributed to the higher percentage of those falling below the 140/90 target (Maksymets et al. 2019). As well Wang et al. (2013) indicated that Simvastatin can increase the vasodilatory nitric oxide in the serum of coronary heart disease complicated congestive heart failure patients. FLC had no impact on lowering systolic or diastolic pressures (Barre et al. 2012) in older T2D patients but Cornish et al. (2009) observed a decrease in diastolic pressure as the result of FLC consumption in persons with metabolic syndrome. There appear to be no reports of CAs or HMGA preventing or managing hypertension in PT2D or T2D onset in animals or humans. However, it may be that CAs or HMGA, via dyslipidemia management may reduce atherosclerosis and hence manage hypertension in PT2D or T2D.

Dyslipidemia

Guclu et al. (2004), using Pravastatin in metabolic syndrome patients, showed a drop in total plasma cholesterol, low-density lipoprotein cholesterol (LDLc), and triglycerides with an increase in high-density lipoprotein cholesterol (HDLc) with Jula et al. (2002) showing the same effects in serum after Simvastatin administration in T2D patients. Scharnagl et al. (2004) noted that Cervivastatin lowered serum total cholesterol, LDLc and small dense (sd)-LDLc in T2D patients with increased sd-LDLc. Sone et al. (2002) did not report serum sd-LDL-c but did show a drop in the proportion of sd-LDL, relative to total LDL, in T2D patients taking Pitavastatin. Ikezaki et al. (2020) have noted the importance of sd-LDLc and LDLc in causing atherosclerotic progression. Atorvastatin, increased plasma LDL size in T2D patients though there was no mention of sd-LDLc (Pontrelli et al. 2002). Increased LDL size proportion reduces atherosclerosis (Hulthe et al. 2000). However, Barre et al. (2012) did not show a change in plasma sd LDLc in older T2D patients consuming FLC; that said, the cholesterol content of sd-LDL may not be tied to the relative proportion of sd-LDL particles to total LDL particles. Cornish et al. (2009) observed no change in fasting serum total cholesterol, triglycerides, the total cholesterol:HDLc ratio, HDLc or LDLc as the result of FLC consumption in persons with metabolic syndrome. FLC consumption was without impact on any aspect of dyslipidemia (Pan et al. 2007; Barre et

al. 2012) in T2D, though in the case of Barre et al. (2012), patients were not hypercholesterolemic while those in the Pan et al. (2007) study were hypercholesterolemic; it could be that the CA and/or HMGA dose/length of time given was insufficient to alter the identified lipids. However, plasma cholesterol and LDLc lowering has been observed (Zhang et al. 2008), in non-diabetic hypercholesterolemic persons consuming FLC though the contribution of CAs or HMGA to cholesterol lowering has not been elucidated in FLC consumers. Hallund et al. (2006) looked at FLC administered to healthy post-menopausal females with normal lipid blood serum levels and found no change in HDLc, LDLc, cholesterol and triglycerides. CA decreased plasma cholesterol, LDLc and triglycerides and increased plasma HDLc in db/db mice (Yoo et al. 2012) and decreased serum cholesterol and triglycerides in alloxan-induced T2D rats (Wang et al. 2015). Thus, again, CAs or HMGA, if given in sufficient dose and length of time, may be hypercholesterolemic/antidyslipidemic agents (Prasad 1999, 2005; Yoo et al. 2012; Wang et al. 2015). As HMG-CoA R is the rate limiting enzyme in cholesterol synthesis, its inhibition very effectively decreases cholesterol synthesis as demonstrated in rat hepatic tissue (*in vitro*) (Beg and Lupien 1972) and hence lowers hepatic cholesterol as demonstrated in rats (*in vivo*) (Beg et al. 1968) and serum cholesterol in rats (Beg and Siddiqi 1968) and as such may contribute to lowering plasma cholesterol in some FLC consumers. Indeed, Lupien et al. (1979) found that 2250 mg of HMGA/day for 8 weeks in heterozygous familial hypercholesterolemia patients significantly lowered plasma cholesterol and LDLc with no effect on triglycerides though these patients had not been diagnosed with PT2D or T2D. Lupien et al. (1978) observed a decrease in plasma cholesterol in one non-diabetic homozygous familial hypercholesterolemic patient taking 1500 and 3000 mg of HMGA/day combined with diet therapy for an undisclosed time period. Lupien et al. (1973a) found decreases in serum cholesterol three patients with Frederickson type II hyperlipoproteinemia patients taking HMGA. There was no mention of inability to tolerate HMGA, side effects or contraindications in the Lupien et al. (1973a,b, 1978, 1979) studies except for transient elevations of serum triglycerides in 2 of 3 patients reported by Lupien et al. (1973a); elevated triglycerides can be a problem as they increase atherosclerotic risk (Hsueh and Law 1998) in PT2D and T2D due to such elevation causing decreased increased sd-LDLc (Nikolic et al. 2013; Hirano 2018) and decreased HDLc (Calabresi et al. 1990) as well as the risk of developing T2D (Tirosh et al. 2008). Thus,

Table 1
Impact of selected 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors on the cluster of seven¹

Nature of Study	Central Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human PT2D	Statins FLC CAs HMGA	Statins-yes Pravastatin ⁶ FLC-negative ⁷ CAs HMGA	Statins-yes Pravastatin ^{6,17} FLC-yes-diastolic ⁶ CAs HMGA	Statins-yes Pravastatin ^{6,17} FLC-negative ⁶ CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA
Human T2D	Statins FLC-yes ² CAs HMGA	Statins Atorvastatin worsens Pitavastatin improves Pravastatin no adverse effect ^{8,9} FLC-yes ² CAs HMGA	Statins FLC-negative ² CAs HMGA	Statins-yes Cervastatin Pitavastatin Atorvastatin Simvastatin ^{10,18,19} FLC-negative ^{2,20} CAs HMGA	Statins-yes but Simvastatin may increase thrombosis ^{33,34} FLC-yes ² CAs HMGA	Statins-yes ³⁷ FLC-negative ² CAs HMGA	Statins-yes ⁴¹⁻⁴³ Atorvastatin and Simvastatin ^{44,45} FLC-yes ^{2,46} CAs HMGA
Human non-PT2D or non-T2D	Statins negative ³ FLC CAs HMGA	Statins Atorvastatin and Simvastatin worsen ^{3,10} FLC CAs HMGA	Statins Atorvastatin ⁹ FLC CAs HMGA	Statins-yes FLC-positive ²¹ and negative results ²² CAs HMGA-yes ²³⁻²⁸	Statins FLC CAs-yes- <i>in vitro</i> ³⁵ HMGA	Statins-yes Simvastatin may lower antioxidant potential ¹⁰ FLC CAs HMGA	Statins yes ⁴³ FLC yes ⁴⁷ CAs HMGA
Animal PT2D	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA
Animal T2D model	Statins FLC CAs HMGA	Statins FLC CAs-yes ¹¹⁻¹⁴ HMGA	Statins FLC CAs HMGA	Statins FLC CAs-yes ^{11,13} HMGA-yes ²⁹	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA
Animal non-pre- or post-onset T2D	Statins FLC CAs yes ⁴ HMGA-yes ⁵	Statins FLC CAs HMGA-yes ¹⁵	Statins FLC CAs HMGA	Statins FLC CAs HMGA-yes ³⁰⁻³²	Statins FLC CAs-yes- <i>in vitro</i> ³⁶ HMGA	Statins FLC CAs-yes ³⁸ HMGA- may reduce antioxidant potential ³⁹	Statins Simvastatin Pravastatin Rouvastatin ^{48,49} FLC CAs-yes ⁵⁰ HMGA
Cell culture	Statins FLC CAs HMGA	Statins FLC CAs-yes ¹⁶ HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins FLC CAs HMGA	Statins Pravastatin ⁴⁰ FLC CAs HMGA	Statins FLC CAs HMGA

Abbreviations: CAs – cinnamic acids; FLC – flaxseed lignan complex; HMGA – 3-hydroxy-3-methyl-glutaric acid; PT2D – pre-onset type 2 diabetes; T2D – type 2 diabetes. ¹blank beside statins, FLC, CA, or HMGA means no studies found; otherwise yes (for beneficial findings) or negative findings are noted; ²Barre et al. 2012; ³Maksymets et al. 2019; ⁴Mnafgui et al. 2015; ⁵Yousufzai and Siddiqi 1977; ⁶Yamagishi et al. 2006; ⁷Cornish et al. 2009; ⁸Yamakawa et al. 2008; ⁹Cui et al. 2018; ¹⁰Jula et al. 2002; ¹¹Yoo et al. 2012; ¹²Cicero and Colletti 2016; ¹³Wang et al. 2015; ¹⁴Hafizur et al. 2015; ¹⁵Wetherup et al. 1995; ¹⁶Prabhakar and Doble 2011; ¹⁷Guclu et al. 2004; ¹⁸Scharnagl et al. 2004; ¹⁹Pontrelli et al. 2002; ²⁰Pan et al. 2007; ²¹Zhang et al. 2008; ²²Hallund et al. 2006; ²³Beg et al. 1968; ²⁴Beg and Siddiqi 1968; ²⁵Lupien et al. 1973a; ²⁶Lupien et al. 1973b; ²⁷Lupien et al. 1978; ²⁸Lupien et al. 1979; ²⁹Francesconi et al. 1987; ³⁰Yousufzai and Siddiqi 1976a; ³¹Kahn et al. 1972; ³²Yusufi and Siddiqi 1974; ³³Perego and Davi 2012; ³⁴Postula et al. 2012; ³⁵Hubbard et al. 2003; ³⁶Kim et al. 2010; ³⁷Ohara et al. 2018; ³⁸Lee et al. 2007; ³⁹Frank et al. 2004; ⁴⁰Ceolotto et al. 2006; ⁴¹Lodovici et al. 2015; ⁴²Schonbeck and Libby 2004; ⁴³Paradela-Dobarra et al. 2013; ⁴⁴Milajerdi et al. 2020; ⁴⁵Lee et al. 2002; ⁴⁶Pan et al. 2009; ⁴⁷Hallund et al. 2008; ⁴⁸Sukhova et al. 2002; ⁴⁹Kim et al. 2019; ⁵⁰Anlar et al. 2018.

caution with HMGA must be noted though transiency of elevated triglycerides may not be an issue. However, there are no other reports of HMGA-driven elevated triglycerides so the two patients may not be representative of a larger patient population. In streptozotocin-diabetic rats, HMGA did not significantly increase plasma HDLc though there was a trend toward an increase in such (they also noted a significant decrease in plasma cholesterol and triglycerides as the result of HMGA administration) (Francesconi et al. 1987). HMGA lowered serum total triglyceride and cholesterol and cholesterol and triglyceride in serum β -lipoproteins in Triton WR-1339 induced hyperlipidemia in rats Yousufzai and Siddiqi (1976a). Khan et al. (1972) observed a HMGA-induced lowering of serum cholesterol in non-diabetic rabbits fed an atherogenic diet. Yusufi and Siddiqi (1974) found that HMGA lowered serum and aortic cholesterol and triglycerides in non-diabetic, hyperlipemic male albino rabbits. Consistent with such findings was the observation that HMGA could shrink atherosclerotic lesions in male albino rabbits (Lupien et al. 1973b); unfortunately, such work appears not to have been done in humans. As well, Yousufzai and Siddiqi (1976b) observed aortic arch atheromatous lesion regression in non-diabetic rats as the result of HMGA administration. Such atherosclerosis management is important as atherosclerosis causes myocardial infarction and stroke the two major causes of death in T2D patients (Sasaki et al. 1995; Alberti et al. 2007; Sharma et al. 2017).

Pro-thrombosis

The statins can reduce thrombosis (via reduced inflammation) in T2D patients (Perego and Davi 2012) with Wang et al. (2013) pointing that Simvastatin can increase the plasma levels of anti-platelet aggregatory nitric oxide in non-T2D humans. Despite that finding, Isley et al. 2006 have cautioned that Simvastatin can increase mean platelet volume in T2D patients, such being a potentially contributing factor to increased thrombosis. Postula et al. (2012) have also suggested that statins can reduce platelet reactivity in T2D patients. Barre et al. (2012) showed an increased bleeding time, indicative of decreased platelet aggregability and hence pro-thrombosis, due to FLC consumption in older T2D patients. CA inhibits healthy rat (Kim et al. 2010) and healthy human (Hubbard et al. 2003) *in vitro* platelet aggregation. However, there is no direct evidence of impact or lack thereof of CAs or HMGA on elevated platelet reactivity in PT2D or T2D patients.

Oxidation

Rosenson (2004), in a review paper, demonstrated the LDL antioxidant capacity of statin drugs. As well Ohara et al. (2018) noted less oxidative stress with statin use in T2D patients. Ceolotto et al. (2006) demonstrated in *ex vivo* fibroblasts that Pravastatin could reduce insulin-induced free radicals. As oxidation leads to inflammation (Lodovici et al. 2015; Hussain et al. 2016), it is possible to hypothesize that Pravastatin might do the same in PT2D and T2D. However, Jula et al. (2002) found lower plasma total peroxyl radical-trapping antioxidant potential and increased conjugated diene formation as the result of Simvastatin administration in hypercholesterolemic males. Barre et al. (2012) failed to show a drop in LDL oxidation when FLC was consumed by older T2D patients. This may be a case of inhibitor type (CAs or HMGA) and/or dose and/or duration of treatment not being sufficient to result in lower LDL oxidation. However, CA lowered hepatic malondialdehyde and elevated erythrocyte and hepatic catalase, glutathione peroxidase and elevated erythrocyte glutathione in high cholesterol fed rats (Lee et al. 2007). HMGA appears not to have been studied in terms of oxidation but as it, like the statins, are HMG-CoA RIs and as least some statins lower oxidation (Ohara et al. 2018), HMGA too may lower oxidation, albeit perhaps independent of such inhibition. However, in rats, SDG oligomers with HMGA lowered α -tocopherol and the combination of α -tocopherol and γ -tocopherol in plasma more so than SDG alone (Frank et al. 2004) so caution in using HMGA as an antioxidant is warranted. As well, Fernandes et al. (2013, 2016) found an increase in oxidative stress due to an HMG-CoA lyase deficiency causing elevated HMGA in rat brain tissue, so caution may be warranted in those with such a deficiency. There appears to be no direct evidence of impact of CAs or HMGA on oxidation in PT2D and/or T2D patients. However, individuals who do not adequately clear HMG-CoA due to an HMG-CoA lyase deficiency (Jones et al. 2020) experience increased oxidative stress (dos Santos Mello et al. 2015; da Rosa et al. 2016; Vamecq et al. 2020). In these persons, concomitant consumption of bezafibrate may reduce oxidation (da Rosa-Junior et al. 2020). As well, HMGA is largely metabolized in the kidney and excess plasma levels of HMGA may be an indicator of early-stage renal dysfunction (Nierenberg et al. 2019) so again HMGA would not be appropriate for such individuals with an HMG-CoA lyase deficiency.

Inflammation

Milajerdi et al. (2020), in a review paper indicated that Atorvastatin and Simvastatin in T2D patients could decrease the generalized inflammatory marker (serum C-reactive protein, CRP) with Atorvastatin possibly reducing serum interleukin-6 (IL-6), the principal inducer of the CRP gene (Volanakis 2001). As well, Lee et al. (2002) noted that Simvastatin induced a decrease in plasma CRP levels in T2D patients. Lodovici et al. (2015) indicated that T2D females but not males with complications responded to statin treatment with a lowering of inflammation as measured by decreased plasma CRP. Paradelado-Barro et al. (2013) indicated that unspecified statins use lowered serum high sensitivity (HS)-CRP in study pool of patients with and without T2D.

Diamantis et al. (2017), in a review paper, noted that the anti-inflammatory aspects of some statins can improve the prognosis for coronary artery disease in human including those with post-onset T2D. Schonbeck and Libby (2004) indicated that the statins have an anti-inflammatory role, dependent and independent of statin-induced lipid lowering, but they did not mention PT2D or T2D. Sukhova et al. (2002) noted that Simvastatin and Pravastatin inhibit inflammation in the atheroma of adult male non-diabetic cynomolgus monkeys. Atorvastatin and Rosuvastatin influenced the gut's microbiota composition which correlated with decreased ileal pro-inflammatory interleukin-1 β (IL-1 β) and increased ileal anti-inflammatory transforming growth factor 1 β (TGF-1 β) expression in high fat diet fed C57BL/6N mice (an aged mouse model) (Kim et al. 2019). FLC better managed plasma CRP in healthy post-menopausal women (Hallund et al. 2008) and serum CRP compared to controls in T2D patients (Pan et al. 2009) and reduced plasma CRP in older T2D patients (Barre et al. 2012) but the role of CAs and HMGA contained in FLC is not clear. CA may have anti-inflammatory potential as Anlar et al. (2018) reported it to be an antioxidant in T1D rats. There is nothing in the literature about the use of HMGA to combat inflammation.

Some words of caution regarding certain HMG-CoA RIs

Words of caution are in order in that, controversially (Mogadam 2014; Skoumas et al. 2018), some of the statins have been suggested in some papers increase the incidence of T2D in patients at risk of that pathology (Macedo et al. 2014; Gastaldi and

Philippe 2015; Climent et al. 2017; Li et al. 2018). Indeed, Barkas et al. (2020) noted that the greatest risk of statin-caused T2D is in the metabolically unhealthy obese and metabolically unhealthy non-obese patients with statin treated metabolically healthy obese not being at risk of T2D; however, the metabolically healthy obese can, in a non-statin related manner become metabolically unhealthy (Kouvari et al. 2019), and so caution with statin use must be exhibited in those moving toward a metabolically unhealthy state even though such is not statin-related. Jick and Bradbury (2004) indicated that Pravastatin and Simvastatin do not protect against the development of T2D but gave no indication that those two drugs conferred a greater degree of risk of developing T2D. Jeong et al. (2019) have data to suggest that Pitavastatin may not be of concern in increasing T2D risk but may cause increased calorie and fat consumption (Sugiyama et al. 2014). Riche and McClendon (2007) have indicated that use of statins in T2D patients should be individualized if there is no pre-existing cardiovascular disease and that statins should not be used solely because the patient has T2D. There are, as of yet, no words of caution to date regarding FLC or CAs. There are some concerns with HMGA. Toxic levels of HMGA occur in persons with HMG-CoA lyase deficiency and there is one report of elevated triglycerides in two non-diabetic persons on HMGA. As well, HMGA may lower plasma α -tocopherol and the combination of α -tocopherol and γ -tocopherol and thus possibly reducing anti-oxidant potential.

Conclusion

PT2D and T2D patients require management of the cluster of seven (central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation). Studies suggest that selected HMG-CoA RIs (statins, FLC with CAs and HMGA and each of CAs and HMGA) alone and/or in combination have or may have the potential to influence at least three members of the cluster of seven. The potential for pleiotropic effects of selected statins (hyperglycemia, hypertension and dyslipidemia in PT2D and hyperglycemia, dyslipidemia, pro-thrombosis, oxidation and inflammation in T2D), FLC (central obesity, hyperglycemia, pro-thrombosis and inflammation in T2D), CAs (hyperglycemia and dyslipidemia-animal model T2D only and in non-PT2D and non T2D animals, obesity, hyperglycemia, pro-thrombosis and oxidation) and HMGA (obesity, hyperglycemia and dyslipidemia in non-PT2D or non-T2D animals and

dyslipidemia in non-PT2D or non-T2D humans) may not be solely centered on their HMG-CoA R inhibition ability. However, in PT2D and T2D patients, large scale multi-center clinical trials with short-term and long-term agent exposure analysis for various doses, are lacking to establish their full safety and efficacy in management of the members of the cluster

of seven, as demonstrated by *in vivo* mechanisms by one or more of these agents. Some of the statins and HMGA have some real and/or potential safety concerns. However, contraindications, side effects and drug interactions have yet to be fully established for all the aforementioned HMG-CoA RIs in PT2D and T2D humans. Table 1 summarises this paper.

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