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REVIEW

Use of fibrates in the metabolic syndrome: A review

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Abstract

The use of fibrates in the treatment of dyslipidaemia has changed significantly over recent years. Their role appeared clear at the start of this century. The Helsinki Heart Study and Veterans Affairs High-Density Cholesterol Intervention Trial suggested significant benefit, especially in patients with atherogenic dyslipidaemia. However, this clarity disintegrated following the negative outcomes reported by the Bezafibrate Infarction Prevention, Fenofibrate Intervention and Event Lowering in Diabetes and Action to Control Cardiovascular Risk in Diabetes randomised controlled trials. In this review we discuss these and other relevant trials and consider patient subgroups such as those with the metabolic syndrome and those needing treatment to prevent the microvascular complications associated with diabetes in whom fibrates may be useful. We also discuss observations from our group that may provide some explanation for the varying outcomes reported in large trials. The actions of fibrates in patients who are also on statins are interesting and appear to differ from those in patients not on statins. Understanding this is key as statins are the primary lipid lowering agents and likely to occupy that position for the foreseeable future. We also present other features of fibrate treatment we have observed in our clinical practice; changes in creatinine, liver function tests and the paradoxical high density lipoprotein reduction. Our purpose is to provide enough data for the reader to make objective decisions in their own clinical practice regarding fibrate use.

Key words: Fibrates; Metabolic syndrome; Paradoxical high density lipoprotein cholesterol decrease; High density lipoprotein cholesterol; Cardiovascular disease; Peroxisome proliferator-activated receptor; Randomised control trial; Triglycerides

Core tip: Atherogenic dyslipidaemia is characterised by low high density lipoprotein cholesterol (HDL-C) and raised triglycerides, this pattern being associated with adverse cardiovascular risk. The fibrate class of drugs has been shown to both elevate HDL-C and reduce triglyceride concentrations. Despite several randomised control trials the data remain conflicting in regards to the use of fibrates in cardiovascular disease management. Our objective is to consolidate and summarise the literature to clarify the current evidence base.

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INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death worldwide[1] and in the United Kingdom in 2012, accounted for 28% of deaths[2]. Treatment is based on reducing modifiable risk factors with lowering of serum lipid levels one of the major targets[3]. Despite overwhelming evidence showing that statin-induced reduction of serum low density lipoprotein cholesterol (LDL-C) is associated with a marked reduction in CVD risk[4] there appears to be a high residual risk[5] perhaps due to other lipoprotein particles associated with cardiovascular risk[6-8]. Therefore, additional therapies may be useful to target these atherogenic lipoprotein particles and it is in this context that fibrates could have a useful clinical role. The evidence for this claim will be reviewed.

ATHEROGENIC DYSLIPIDAEMIA, THE METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE

Statins competitively inhibit HMG CoA reductase and thereby effect a decrease in hepatic cholesterol synthesis. This results in the up-regulation of LDL receptors consequently increasing LDL uptake which in turn lowers plasma cholesterol[9]. Following the 4S secondary prevention randomised control trial (RCT) in 1994[10], statins have formed the cornerstone of lipid reduction strategy in CVD prevention guidelines[3,11]. The "lower is better" hypothesis regarding cholesterol and LDL-C levels[4] has been supported by trials including treating to new targets[12], The Reversal of Atherosclerosis with Aggressive Lipid Lowering[13] and Pravastatin or Atorvastatin Evaluation and Infection Therapy[14]. Importantly, studies such as A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden (ASTEROID)[15] and Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin *vs* Atorvastatin (SATURN)[16] suggest even regression of atheromatous plaque is possible if LDL-C levels are lowered sufficiently.

However, despite optimal reduction of LDL-C with statins and, correction of other modifiable risk factors, CVD risk is not eliminated[6]. The source of this residual risk may be due to other atherogenic lipid species such as reduced high density lipoprotein cholesterol (HDL-C) and/or raised triglycerides (TG) which are only modestly affected by statin therapy. The association between CVD and low HDL-C was first reported by Barr *et al*[17] nearly 60 years ago and confirmed in prospective studies such as the Framingham Heart Study[18] and the Munster Heart Study[19,20]. This association appears to be independent of LDL-C[18]. Cardiovascular event rates in statin trials also reflect this; when the study cohort is stratified by HDL-C, HDL-C levels remain associated with CVD even following LDL-C reduction[6]. Elevated TG levels have also been linked with CVD in studies such as multiple risk factor intervention trial and the Copenhagen City Heart Study[7,8].

The lipid profile characterised by low HDL-C and high TG is termed atherogenic dyslipidaemia or the atherogenic lipoprotein phenotype (Table 1). This forms one of the characteristic features of the metabolic syndrome. This syndrome gained global recognition following the Banting Lecture delivered by Reaven[21] in 1988 to the American Diabetes Association. He termed the combination of hypertension, dyslipidaemia and glucose intolerance as syndrome X and suggested that affected individuals were at higher risk of atherosclerosis[21]. The International Classification of Disease code now terms syndrome X, the metabolic syndrome[22]. Various groups have provided classification systems for the metabolic syndrome (Table 1)[23]. These include the World Health Organisation (WHO)[24], European Group for the Study of Insulin Resistance[25], American College of Endocrinology[26], National Cholesterol Education Program - Adult Treatment Panel Ⅲ[27] and, more recently, the international diabetes federation (IDF)[28]. Although the classifying characteristics are the same in these classifications, the thresholds for inclusion differ. A consensus was reached in 2009 with the IDF, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis and the International Association for the Study of Obesity agreeing on threshold levels that mirrored those of the IDF[29].

There is debate as to the clinical usefulness of making a diagnosis of metabolic syndrome. While the syndrome is associated with a doubling of CVD risk[30], much of this increase is the sum of the individual classifying components[31]. Bayturan *et al*[32] reviewed 3459 patients

Table 1 The thresholds defining the metabolic syndrome issued by individual organisations (reproduced from: Strange *et al*[23])

Group	WHO[24]	EGIR[25]	NCEP/ATP Ⅲ[27]	AACE[26]	IDF consensus[28]	IDF consensus (10 to < 16 yr)[112]
Definition	IGT, IFG, T2DM or lowered insulin sensitivity plus 2 of the following	Plasma insulin > 75th percentile plus 2 of the following	3 of the following	IGT or IFG plus any of the following based on clinical judgement	See below	
Europoid waist circumference (cm)	W:H > 0.90 M, W:H > 0.85 F or BMI > 30 kg/m^2	⩾ 94 M, ⩾ 80 F	⩾ 102 M, ⩾ 88 F	BMI ⩾ 25 kg/m^2	⩾ 94 M, ⩾ 80 F or BMI > 30 kg/m^2 plus 2 of the following	> 90th percentile plus 2 of the following
Triglyceride (mmol/L)	> 1.7	> 1.7	⩾ 1.7	> 1.7	> 1.7	⩾ 1.7
HDL (mmol/L)	< 0.91 M, < 1.01 F	< 0.91	< 1.03 M, < 1.29 F	< 1.03 M, < 1.29 F	< 1.03 M, < 1.29 F	< 1.03
BP (mmHg)	⩾ 140/90	⩾ 140/90 or on treatment	⩾ 130/85	⩾ 130/85	SBP ⩾ 130 or DBP ⩾ 85 or on treatment	SBP ⩾ 130 and/or DBP ⩾ 85
Glucose (mmol/L)	IGT, IFG or T2DM	IGT or IFG (but not diabetes)	⩾ 5.6[113] or diabetes	IGT or IFG (but not diabetes)	⩾ 5.6	⩾ 5.6 or known T2DM
Others	Microalbuminuria ACR > 30 mg/g			Other features of IR[1]		

[1]Includes polycystic ovary syndrome, family history or ethnic group susceptible to type 2 diabetes, sedentary lifestyle and advancing age. ACR: Albumin creatinine ration; BMI: Body mass index; DBP: Diastolic blood pressure; F: Female; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; SBP: Systolic blood pressure; M: Male; T2DM: Type 2 diabetes mellitus; W:H: Waist to hip ratio; HDL: High density lipoprotein; WHO: World Health Organisation; NCEP: National cholesterol education program; EGIR: European group for the study of insulin resistance; IDF: International diabetes federation; AACE: American Association of Clinical Endocrinologists.

included in 7 trials using plaque progression measured by intravascular ultrasonography as outcome. Although the metabolic syndrome was significantly associated with increased plaque, the relationship lost significance when adjusted for serum TG, body mass index (BMI), HDL-C, blood pressure value/treatment of hypertension. In the multiple regression model just serum TG concentrations > 1.70 mmol/L remained significantly associated with plaque progression, this perhaps making a further case for fibrate therapy as potent triglyceride reducing agents in hypertriglyceridaemia[32].

Although evidence indicates that the metabolic syndrome does not add prognostic risk in an individual patient, we and others[33] argue that it has practical merit. Awareness of the metabolic syndrome makes it easier to adopt a holistic approach to care rather than focussing on individual risk factors. It may be even more useful in a research setting. The characteristics of the syndrome are associated with each other, but also individually increase CVD risk. Thus, the entire network of risk factors must be considered. Indeed, the various phenotypes of the syndrome prompt the use of specific therapies. For example, the syndrome is characterised by weight gain that may be ameliorated by nutritional advice resulting in weight loss and reduced hypertriglyceridaemia and increased HDL. Such advice and intervention should be first line treatment which is continued throughout treatment even if initial efforts are unsuccessful. Insulin resistance and hypertension may also be improved by this approach. Fibrates, by causing elevation of HDL-C and reduction of TG, may be ideally suited to treating people with this condition. The discovery and action of fibrates will now be described.

DISCOVERY AND DEVELOPMENT OF FIBRATES

Chemically fibrates are based on phenylethyl acetic acid, a derivative of dehydrocholic acid. The compounds were developed as insecticides by imperial chemical industries (ICI) Laboratories in England (the pharmaceutical division is now part of Astra Zeneca) and accidental exposure by farm workers in France in 1953 provided the first observation that they could cause reduction of lipids in serum[34]. This finding was confirmed in rats though the mechanism of cholesterol reduction was unknown[35]. Subsequently, work at ICI identified several oxyisobutyric acid derivatives with similar effects, an observation that lead in 1962 to the development of clofibrate (ethyl-α-4-chlorophenoxyisobutyrate), the first therapeutically useful fibrate[36].

Fenofibrate, which is a benzoyl derivative of clofibrate with higher efficacy, was produced in 1974[37]. In the late 1970's and early 1980's gemfibrozil[38], bezafibrate[39] and ciprofibrate[40] were added to the structurally diverse fibrate family[41]. Clofibrate and fenofibrate are pro-drugs that are hydrolysed to their active metabolites clofibric acid and fenofibric acid respectively, while gemfibrozil and bezafibrate are active compounds. Development of fibrates as a class was hindered by concerns of murine hepatic carcinogenicity thought to be associated with peroxisomal proliferation[42,43]. However, Blümcke *et al*[44], in 1983 demonstrated that humans were not at increased risk of hepatic tumour formation. Clofibrate became non-viable as a therapeutic agent when the WHO cooperative trial, a primary prevention trial, showed a 47% increase in mortality, mainly non-cardiac,

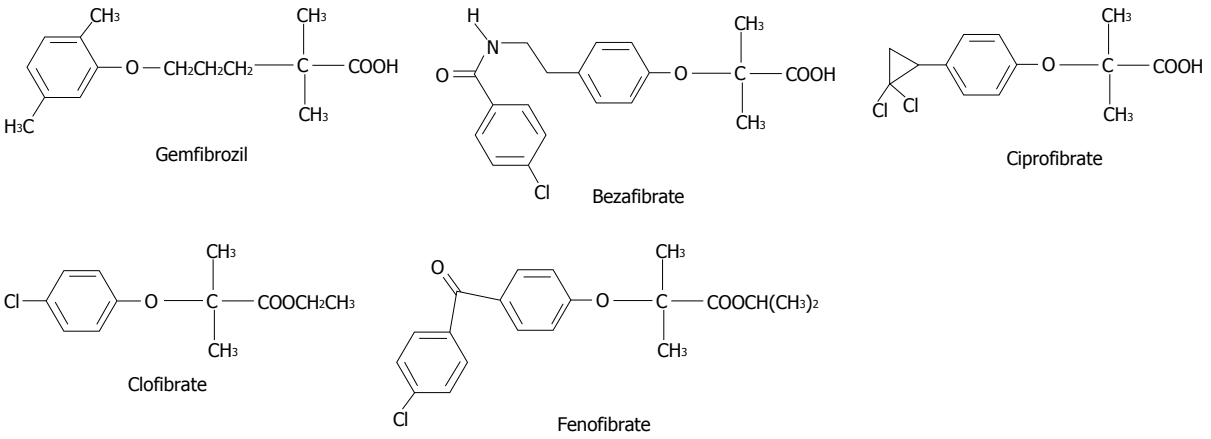

Figure 1 Chemical structures of fibrates that have been used clinically.

in the treatment arm[45]. The other fibrates remain clinically available though their role is under review following variable outcomes in RCTs (see below).

METABOLISM OF FIBRATES

With the exception of gemfibrozil, the role of individual members of the phase 1 detoxifying cytochrome p450 supergene family in the metabolism of fibrates is unclear. Significantly, gemfibrozil inhibits CYP2C8 which is involved in the metabolism of the statin cerivastatin, thereby potentially causing an increase in the plasma concentration of the statin and an increased risk of rhabdomyolysis. Subsequently in 2001, cerivastatin was withdrawn[46]. It is recommended that when treating patients with both a fibrate and statin that gemfibrozil be avoided[47]. Other fibrates in clinical use have not shown a similar interaction with statins. Fibrates also cause reversible elevations in creatinine levels and, though this is not usually a contraindication for use, fibrate dose should be reduced or the drug withheld in those with renal impairment as recommended by the manufacturer[47]. Doses of fibrates should be reduced or withheld in those with renal impairment as per manufacturer's advice. The chemical structures of fibrates in clinical use are shown in Figure 1.

FIBRATE PHARMACOLOGY

Initially, fibrates were thought to work *via* an androsterone-like effect[36] though later it was realised that their therapeutic target was the nuclear peroxisome proliferator-activated receptor (PPAR). Nuclear receptors are one type of receptor capable of recognising external stimuli and effecting internal changes *via* mediation of expression of key genes and hence, protein synthesis. In the 1980's it was recognised that fibrates affect transcription of various proteins associated with lipid metabolism[48,49] and it is now known that PPAR receptors are one of the cell's mechanisms for regulation of energy homeostasis.

PPARα was first cloned in the mouse[50], and this was followed 2 years later by work from Dreyer *et al*[51] who cloned 3 types of PPAR (PPARα, PPARγ and PPARβ/δ) in Xenopus. PPARα has subsequently been identified in other species (*e.g.*, humans, amphibians, teleosts and cyclostomes)[52]. There are structural similarities between the 3 PPAR subtypes. LDL and very LDL (VLDL) activate PPARα in the presence of lipoprotein lipase which suggests that esterified triacylglycerols and fatty acids may be the natural ligands[53].

The PPAR-retinoid X receptor (RXR) heterodimer exists in active and inactive states. When inactive it is bound to co-repressors such as the nuclear receptor co-repressor or the silencing mediator for retinoid and thyroid hormone receptors. When a ligand binds to either PPAR or RXR a conformational change in the heterodimer takes place and the co-repressor dissociates in order for the complex to bind and activate co-activators such as the steroid receptor co-activator 1. When the PPAR-RXR complex is activated it binds to the peroxisome proliferator response element found in the upstream region of target genes[54] and induces transcription.

Fibrates bind and activate PPARα and regulate gene expression, thereby influencing fatty acid and lipoprotein metabolism in liver, muscle, both skeletal and cardiac, and kidney[55]. Synthesis of apoprotein (Apo)-AⅠ, Apo-AⅡ, ApoC-Ⅲ, lipoprotein lipase, ATP-binding cassette transporter A1, cholesterol ester transfer protein, scavenger receptor class B-type 1 and ApoA5[56-58], factors mainly controlling HDL and VLDL metabolism, are altered by activated PPARα. Thus, fibrate therapy leads to increased HDL-C concentrations, a greater reduction in TG levels and a modest decrease in LDL-C concentrations[59]. Fibrates also have a role in preventing the hypertriglyceridaemia associated with pancreatitis. Guidelines do suggest fibrates as first-line TG lowering treatment to reduce the risk of pancreatitis, with nicotinic acid, omega 3 supplements and statins also considered[60].

The clinical efficacy of fibrates in CVD risk management will now be examined.

Table 2 Details of the large fibrate outcome trials in the total cohort are provided in this table

Trial	HHS	VA-HIT	BIP	FIELD	ACCORD
Drug	Gemfibrozil	Gemfibrozil	Bezafibrate	Fenofibrate	Fenofibrate
Dose	1200 mg/d	1200 mg/d	400 mg/d	200 mg/d	200 mg/d
Primary endpoint	MI (fatal and non-fatal), cardiac death	Combined incidence of nonfatal MI and death from CAD	MI (fatal and non-fatal), sudden death	CHD death, non-fatal MI	Non-fatal MI, non-fatal stroke, or CVD death
Mean follow-up (yr)	5	5	6	5	5
Patients (total)	Fibrate = 2051; placebo = 2030	Fibrate = 1264; placebo = 1267	Fibrate = 1548; placebo = 1542	Fibrate = 4895; placebo = 4900	Fibrate = 2765; placebo = 2753
Effect on Lipids (% change from baseline)	LDL-C: -10; TC: -11; TG: -43; HDL-C: +10	LDL-C: 0; TC: -4; TG: -31; HDL-C: +6	LDL-C: -6.5; TC: -4.5; TG: -21; HDL-C: +18	LDL-C: -12; TC: -11; TG: -29; HDL-C: +5	LDL-C: -19; TC: -14; TG: -22; HDL-C: +8.4
Outcomes	CHD: ↓ 34%; non-fatal MI: ↓ 37%; total mortality: No change	CHD and non-fatal MI: ↓ 22%; total mortality: ↓ 11% (NS)	Fatal and nonfatal MI and sudden death: ↓ 9% (NS); total mortality: No change	CHD and non-fatal MI: ↓ 11% (NS); total mortality: ↑ 19% (NS)	Nonfatal MI nonfatal stroke CVD death: ↓ 8% (NS); total mortality: ↓ 9 % (NS)

HHS: Helsinki Heart Study; VA-HIT: Veterans Affairs High-Density Cholesterol Intervention Trial; BIP: Bezafibrate Infarction Prevention; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; CVD: Cardiovascular disease; NS: Not significant; LDL-C: Low density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; MI: Myocardial infarction; CAD: Coronary artery disease; CHD: Coronary heart disease.

FIBRATE INTERVENTION TRIALS: GEMFIBROZIL

There is a theoretical basis behind the hypothesis that fibrates would be a useful adjunct in CVD risk management; epidemiological studies indicate their value in the treatment of the atherogenic dyslipidaemia associated with CVD risk. However, published data are conflicting. RCTs with gemfibrozil[61,62] have shown overall benefit while those using fenofibrate[63,64] and bezafibrate[65] have been negative in terms of the primary end point. Details of these trials including the primary end points are presented in Table 2. Clearly, these data are very different to those obtained from trials using statins; all members of that drug group demonstrate CVD risk-lowering effects. The larger fibrate RCTs will be described and reasons suggested for these discrepancies.

Considering the positive gemfibrozil studies first, the helsinki heart study (HHS) lasted for 5 years and studied a large cohort of men comparing 600 mg gemfibrozil twice daily against placebo (2051 and 2030 men respectively). Inclusion criteria included adult men aged 40-55 years with a non-HDL-C > 5.2 mmol/L[61]. The mean LDL-C of the study group was 4.88 mmol/L[66]. The comparison of relative risk in cardiovascular outcomes demonstrated a 34% statistically significant reduction with fibrate therapy; 27.3 events in the gemfibrozil and 41.4 events in the placebo group per 1000 individuals[61]. Prior to the widespread use of statins this was a simple comparison of fibrates against no other lipid lowering therapy. Subgroup analysis demonstrated that those with an elevated TG and reduced HDL-C level had greater relative risk reduction providing the first evidence that fibrates may be most useful in those with atherogenic dyslipidaemia[67].

The second large, gemfibrozil study (2531 participants), the Veterans Affairs High-Density Cholesterol Intervention Trial (VA-HIT), selected patients with established coronary disease[62]. Completed over 10 years after the HHS this again compared gemfibrozil (1200 mg/d) *vs* placebo and only in men. Inclusion age was higher, selecting those aged < 74 years, and low HDL-C < 1.0 mmol/L. LDL-C was not affected by treatment, but HDL-C was elevated by 6% and TGs decreased by 31% and total cholesterol (TC) by 4% when compared to placebo. The primary outcome in this secondary prevention RCT was myocardial infarction or cardiovascular death. It is also worth noting that the LDL-C of the cohort was below 3.6 mmol/L, in an attempt to negate LDL-C related CVD risk. The median follow-up was 5.1 years and during this period the relative risk was significantly reduced by 22% in the treatment group (absolute event rate was 17.3% in the treatment *vs* 21.7% in the placebo control arms), and even more so in individuals with features of insulin resistance when a sub group analysis was carried out[62].

FIBRATE INTERVENTION TRIALS: FENOFIBRATE

The clinical usefulness of Fenofibrate has been assessed in 2 large RCTs; the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD-LIPID) trials[63,64]. The FIELD trial was the larger and selected only patients with type 2 diabetes mellitus. In total, 9795 participants (4895 given fenofibrate and 4900 placebo) aged between 50-75 years were enrolled and followed up for a mean of 5 years; 2131 participants had a previous history of CVD. Unlike VA-HIT, which used low HDL-C as an inclusion criterion[62], TG were the primary lipid type with either the TG/HDL-C ratio (≥ 4.0) or TG (1.0-5.9 mmol/L) level defining inclusion. In addition TC had to between 3.9-6.5 mmol/L and those with plasma creatinine > 130 μmol/L were excluded. A non-significant difference in coronary events, the primary outcome was observed; 5.2% participants in

the fenofibrate arm and 5.9% in the control arm[63].

Interpretation of these data are complicated by the addition of statin therapy during the follow-up to any individual not satisfying the TC and LDL-C targets due to the evidence based change in practice at the time (2002 - publication of the heart protection study)[68]. This resulted in different rates of statin treatment; 17% in the placebo and 8% in the fenofibrate arms. This discrepancy could have masked any benefits gained from fenofibrate therapy and, effected changes in the lipid profile. In the fenofibrate treatment group reductions of TC by 11%, LDL-C by 12%, and TG by 29%, with an increase in HDL-C of 5% after 4 mo, were observed (the improvement in HDL-C dropped from 5% to 2% at the end of the 5 years, the reasons for this are unclear)[63].

In a *post hoc* examination of the FIELD study data, 80% of the cohort met the criteria for metabolic syndrome[27,69]. CVD events were significantly reduced in those with low HDL-C, hypertension and most of all in those with marked atherogenic dyslipidemia (27% relative risk reduction, number needed to treat to prevent one coronary event was 23)[69].

Similar to the FIELD study, the ACCORD-LIPID also examined the effects of fenofibrate in those with type 2 diabetes mellitus and an HbA1c $\geqslant$ 7.5% (58 mmol/mol). Published 5 years (2010) after the FIELD study, statin therapy based on LDL-C targets was now well established and therefore, the study was designed to examine whether additional benefit could be gained from adding fenofibrate to simvastatin therapy. With fewer patients than FIELD, 5518 patients, on open-label simvastatin with or without established CVD, were randomised to fenofibrate (2765) or placebo (2753). Age criteria was 40-79 years for those with CVD and increased to 55-79 years for those with 2 additional CVD risk factors followed up for a mean of 4.7 years. When glycated haemoglobin was $\geqslant$ 58 mmol/mol together with established CVD the age at entry was restricted to 40-79 years[64].

The range of LDL-C was 1.55-4.65 mmol/L and HDL-C was < 1.42 mmol/L for women and < 1.29 mmol/L for men; TGs were < 8.5 mmol/L for those in the treatment arm and < 4.5 mmol/L for those on placebo. LDL-C reduction was similar in the treatment and placebo arms but HDL-C was significantly increased, albeit only to a small degree (0.09 mmol/L *vs* 0.06 mmol/L), and TGs significantly lower (0.47 mmol/L *vs* 0.18 mmol/L) in the treatment arm. First occurrence of the primary outcome, non-fatal myocardial infarction or stroke or death from cardiovascular causes, was not significantly different being 2.2% in the treatment arm compared with 2.4% in the placebo. Secondary outcomes, individual components of the primary outcomes and a composite of the primary outcomes including total mortality, revascularisation and admission to hospital for heart failure, were also not significantly different[64].

The diabetes atherosclerosis intervention study (DAIS), non-clinical endpoint trial, coronary artery atherosclerosis progression on angiogram, with fenofibrate looked at 418 men and women (207 and 211 subjects in the fenofibrate group and placebo groups respectively) with type 2 diabetes (mean HbA1c: 48 mmol/mol) with at least one demonstrable coronary lesion. This small trial did show a significantly slower rate of atherosclerosis progression but was not powered towards clinical outcomes[70]. Davidson *et al*[71], in the Fenofibrate Reducing Residual Risk on Statin Therapy trial, also examined a non-clinical endpoint, carotid intimal thickening, in participants on atorvastatin with 342 randomised to placebo and 340 patients to fenofibrate. Inclusion criteria included a dyslipidaemia and history of vascular disease. Unlike DAIS, no significant difference was found in endpoint between the treatment groups[71].

FIBRATE INTERVENTION TRIALS: BEZAFIBRATE

A large bezafibrate RCT, the Bezafibrate Infarction Prevention (BIP) study, studied a secondary prevention population, previous myocardial infarction or angina, over 6.2 years. A total of 3090 men and women aged 45-74 years were randomised to bezafibrate 400 mg *vs* placebo with starting TC 4.7-6.5 mmol/L and HDL-C $\leqslant$ 1.17 mmol/L, TG $\leqslant$ 3.4 mmol/L, and LDL-C $\leqslant$ 4.65 mmol/L. Non-significant reductions in myocardial infarctions (both fatal and non-fatal) and sudden death occurred in the treatment arm (13.6%) *vs* placebo (15%). Treatment did however, increase HDL-C by 18% and reduce TG by 21%[65].

Subgroup analysis of the BIP study data demonstrated a significant and large reduction (almost 40%) in the primary end point, reduction of fatal or non-fatal myocardial infarction or sudden death, in those with TG $\geqslant$ 2.26 mmol/L[65]. When longer term data and subgroup analysis used in a *post hoc* analysis focused on those with 3 of the 5 risk factors classifying the metabolic syndrome (HDL-C, TG, glucose, BMI and blood pressure), the myocardial infarction and non-fatal myocardial infarction rates were significantly lower as was cardiac mortality[72].

In contrast, a smaller double blinded placebo control trial, Bezafibrate Coronary Atherosclerosis Intervention Trial, besides showing significant increases in HDL-C and decreases in TC, TG, VLDL and fibrinogen, did show significant reduction in coronary event rate. This was mirrored by angiographic improvements assessed by mean minimum lumen diameter. This study selected only males under 45 years of age with dyslipidaemia who had survived a myocardial infarction[73].

Meade *et al*[74] in 2002 recruited 1568 patients with lower extremity arterial disease; 783 of these patients were randomised to bezafibrate. The primary outcome measures (coronary heart disease and stroke), as in the BIP trial, did not show a significant change. The secondary outcomes, such as non-fatal coronary events, were significantly reduced. Further, there was

possible reduction in the severity of claudication. The median value of HDL-C of the study group was relatively high (> 1.1 mmol/L), with median TC of 5.6 mmol/L and median TG between 2.1-2.2 mmol/L in placebo and treatment arms. It may be thought that patients with such values would be better treated with statins, even at the point of recruitment into the study. We do concur with this view. Interestingly significantly more participants in the placebo group dropped out due to being started on a statin than those in the treatment arm[74]. This open label nature of the study design leading to unequal treatment with statins between the treatment and control groups, like in the FIELD study, could have influenced the outcome.

Thus, we have several large non-gemfibrozil trials that did not show benefit. Many authors have noted discrepancy between study outcomes, procedures and populations. The open label regarding statin addition (proportions of patients on statins were different between the arms) in the FIELD study and the complicated inclusion criteria seen in the ACCORD-LIPID trial make it difficult to draw conclusions with certainty. The crucial question as to whether fibrates have any role in CVD management remains unanswered except, perhaps in those with marked hypertriglyceridaemia. Sub-group analysis suggests a role for fibrates, but is complicated by lack of study power to detect multiplicity and heterogeneity of treatment effects therefore must be cautiously weighed against[75].

META-ANALYSIS OF FIBRATE TRIALS

Subgroup analysis suggests a benefit from using fibrates in those with the metabolic syndrome[67,69,72,76]. It will, however, need another RCT with narrower inclusion criteria to confirm this benefit. Could this benefit be confirmed by meta-analysis of the existing data? One such study of 5 large trials saw a significant reduction of 28% in cardiovascular risk in those with atherogenic dyslipidaemia, compared with 6% (non-significant) in the comparator group. The study selected only those with HDL-C < 0.91 mmol/L and TG > 2.2 mmol/L, approximately 11%-33% of the trial participants in the 5 trials[77].

A larger meta-analysis, published following the ACCORD-LIPID study[64], summarised 40 years of fibrate outcome data[78]. Major cardiovascular events (myocardial infarction and cerebrovascular events), coronary events, coronary revascularisation, stroke, heart failure, cardiovascular deaths and new-onset albuminuria were the outcomes together with side effects. Studies were identified from Medline, Embase and the Cochrane Library database and filtered down to 18 trials comprising 45058 individuals. Mortality from any cause was not significantly reduced but major cardiovascular events were, the greatest effect occurring in trials with higher mean TG levels. There did not appear to be any difference between trials with regards to baseline HDL-C concentrations, type of fibrate or dose used in the trials[78].

Other potential factors effecting fibrate efficacy

Interestingly there was concern about excess risk in women for the primary outcome (first occurrence of non-fatal myocardial infarction, stroke or death from cardiovascular causes) raised by the ACCORD-LIPID study[64]. Sub-group analysis, of the FIELD data however, did not confirm excess risk in women given fenofibrate, instead it suggested that the fibrate may be more efficacious in women compared to men[79].

There is also conflict with regard to which patients gain most benefit from fibrate use: Patients treated for primary or secondary prevention, specific age groups and co morbidities (*e.g.*, diabetes). In sub-group analysis of the HHS data, the 628 participants with suspected coronary heart disease who were excluded from the original study[61], showed no benefit from gemfibrozil, this finding at odds with that from the main study group[80]. However this finding was compatible with the findings of the BIP trial of bezafibrate[65]. Using ECG data in the FIELD cohort, sub-group analysis revealed that those who had had a silent myocardial infarct gained substantially more benefit from fenofibrate than those who had not with regards future cardiovascular events[81]. In a study of individuals with peripheral vascular disease (LEADER study), sub-group analysis suggested that the younger the patient (< 65 years) the more benefit (reduced coronary events) from bezafibrate[74]. Those with diabetes appear to have more favourable outcomes from fibrate treatment[61-63,70]. However, other studies have not confirmed these findings[64,71] though LDL-C levels varied between the studies.

It has also been suggested that those with a higher baseline LDL-C may benefit from HDL elevating therapies, such as fibrates, more than those with a lower starting level[82]. In a meta-analysis of therapies (including fibrates) that reduced non-HDL-C and raised HDL-C, non-fatal myocardial infarction occurrence was reduced significantly by treatment, but, when studies that included those with low LDL-C were examined, the reduction was only significant in those with high LDL-C at baseline. Kuhnast *et al*[82] went on to demonstrate that the reduction in non-fatal myocardial infarction appeared to be associated with reduction in LDL-C and was not associated with any elevation in HDL-C[82]. This raises the question, if LDL-C levels are reduced sufficiently is there a requirement for additional lipid lowering therapy? However, as we have stated previously, residual risk following LDL-C reduction appears high in patients with low HDL-C. The ACCORD-LIPID trial suggests that this risk may not be reduced by fibrates[64]. An understanding of the effect on lipids, of statin/fibrate combination therapy is essential before reaching conclusions. Our work described later will suggest some interesting patterns that need further study.

Effects of fibrates on microvascular complications

The sequelae of atherosclerotic disease include both

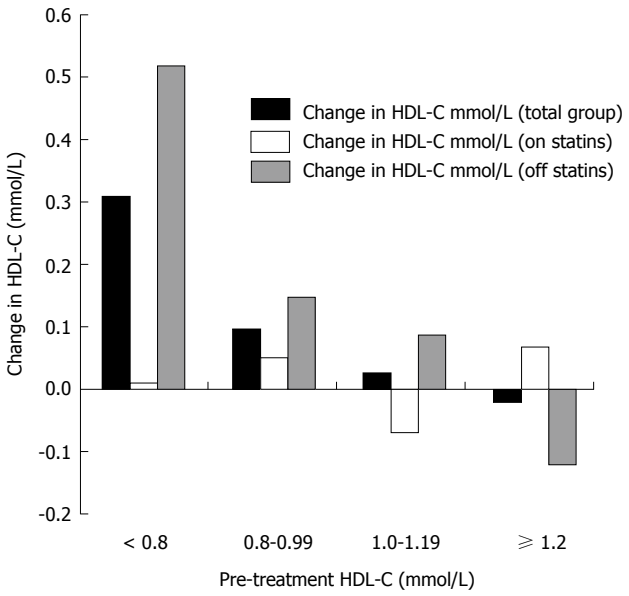

Figure 2 Change in high-density lipoprotein cholesterol following fibrate treatment stratified by pre-treatment high-density lipoprotein cholesterol concentrations in 248 patients (adapted from Ramachandran *et al*[86]) - permission received *via* Rightslink. HDL-C: High density lipoprotein cholesterol.

macrovascular and microvascular damage. So far, we have considered the evidence for macrovascular effects though there are data to suggest that fibrates may affect microvascular outcomes. The first study that demonstrated microvascular benefit was the FIELD study which demonstrated a significant reduction in the rate of progression of albuminuria. In those on fenofibrate, the albuminuria improved[63]. Creatinine levels were also lower in the original treatment group, when off treatment in a wash-out study 5 years later. The microvascular benefit was maintained with less deterioration and progression of albuminuria with improvement continuing in some[83]. Microalbuminuria and macroalbuminuria development were also significantly reduced by fenofibrate in ACCORD-LIPID trial in line with the FIELD study data[64].

Microvascular eye complications have also been studied; in the FIELD study the number of participants requiring laser application for proliferative retinopathy or macular oedema was recorded. There was a significant decrease in laser therapy for retinopathy in those treated with fenofibrate[84]. The ACCORD-Eye study looked at secondary outcome data to study factors that might reduce the progression of diabetic retinopathy[85]. This analysis demonstrated that fenofibrate in addition to simvastatin and intensive glycaemic control, but not intensive blood pressure control, were significantly effective[85]. Therefore, there are data indicating microvascular benefit from fibrates though studies designed to examine microvascular complications as primary endpoints would be beneficial in helping characterise the patient groups to whom benefit would apply.

Thus far we have seen no clear and irrefutable evidence for fibrate use, particular for CVD. There is however, a tantalising suggestion that treatment of patient subgroups such as those with atherogenic dyslipidaemia and other vascular disease complications including nephropathy and retinopathy, may benefit from treatment with fibrates. The role of fibrates in a post-statin world with a plethora of other CVD drugs is unclear. Though lacking the clarity of double-blinded RCTs there is a wealth of experience of fibrate use and such data can add weight to current theories and identify areas that should be studied in the future. We now describe some observations made by our group that may help explain the current confusion. We will also identify potential roles for fibrates and also highlight suggested work that is required in the future.

OBSERVATIONS MADE BY OUR RESEARCH GROUP

By 2006, with the publication of the BIP and FIELD studies it became clear that fibrate treatment was associated with inconsistent results. Hence, we established a programme to investigate the metabolic effects of fibrates in an out-patient setting (with about 7000 clinic visits per annum) at the Heart of England Foundation NHS Trust. In addition to changes in lipids we collected data on liver and renal function. We also have collected data on the rare paradoxical change in HDL-C that is seen following fibrates and thiazolidinedione (PPARγ agonists) treatment.

As shown above, analysis of the large RCTs has suggested possible subgroup benefit from fibrate use in those with low pre-treatment HDL-C levels and elevated TG. Our work would support this with HDL-C increase and TG reduction associated independently with lower HDL-C level and higher TG pre-treatment levels respectively[86,87]. A significantly greater increase was seen in HDL in this cohort when comparing participants with entry HDL-C < 1.0 mmol/L *vs* ⩾ 1.0 mmol/L, but not in those also on statins. The association between HDL-C change and baseline HDL-C (stratified) following fibrates in 257 patients is seen in Figure 2. It is clear that the association is evident only in patients not on statin treatment. These data could support a recommendation that fibrates be reserved for those with low HDL-C[86]. Similarly HDL-C levels, after 6 mo of fenofibrate treatment, were also described in 1994 as being greatest in patients with lower pre-treatment HDL-C, although the nature of the association was not well characterised. Mean increase, in 1334 patients, of HDL-C was significant in the total cohort but larger in those with a baseline HDL-C ⩽ 0.91 mmol/L; 15.2% *vs* 37.9%[88]. Our data suggest that those with high TG may also gain most benefit in TG reduction. This relationship between baseline TG and TG change was not affected by statin treatment. Our series also suggested that TG reduction, while associated with baseline TG levels, was independent of the baseline HDL-C[87].

Both the above findings support the subgroup

analyses from the RCTs; maximum CVD risk reduction being observed in patients with low HDL-C and or elevated TG levels. However, our data indicates that concurrent statin treatment may lead to a more complex pattern. Our results suggest that the specific benefit from fibrates in patients also treated with statins may lie with TG reduction and not an increase in HDL-C as both changes appear to be independent[87]. Our finding is complemented by a recent retrospective study by Scholz *et al*[89] which highlighted the risk posed by elevated TG levels in the metabolic syndrome and pointed to TG lowering by fibrates and omega 3 fatty acids being potentially an important mechanism of cardiovascular event reduction.

The loss of the above association between baseline HDL-C and HDL-C increase (no significant change in HDL-C was observed following fibrates in patients also on statins) in the statin treatment group may be significant in explaining the outcome of the FIELD[86]. As we have mentioned previously in the FIELD study more individuals in the placebo group were on statins[63]. It is interesting to speculate whether the actions of fibrates are altered by statins. This could also have a bearing on the outcome seen in the ACCORD-LIPID trial[64]. Over the past 20 years statins have been the principal lipid lowering agent for CVD risk reduction[3,11]. It is extremely unlikely therefore, that fibrates would form the first line intervention in any future CVD guidance. Thus, it is worth further investigating the effects of fibrates on lipids when combined with a statin. The ACCORD-LIPID[64] trial did this, but we suggest that the group of patients with the atherogenic lipoprotein pattern be further investigated regards lipid and lipoprotein changes.

A measure of HDL function/cholesterol efflux as opposed to HDL-C change in various patient subgroups including those also on statins would also be useful in view of the findings of Rohatgi *et al*[90]. When they analysed the data from the Dallas Heart Study it was seen that the relationship between baseline HDL-C and atherosclerotic CVD was not significant [hazard ratio (HR) = 1.08, 95%CI: 0.59-1.99] when adjusted for other traditional risk factors (age, gender, race, diabetes, hypertension, smoking status, BMI, TC, TG and statin use) and HDL particle concentration after a median follow-up of 0.4 years. However, in a similar model, adjusted for the same variables and HDL-C the highest quartile of cholesterol efflux capacity was significantly associated with CVD in comparison with the lowest quartile (HR = 0.33, 95%CI: 0.19-0.55)[91]. Thus, we suggest that another dimension has to be added when fibrates are investigated in the future, HDL function should also be looked at in addition to concentration.

Our work examining the role of fibrates in those with conditions related to the atherogenic dyslipidaemia or metabolic syndrome, such as in the treatment of non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), is suggestive of benefit. Not only have liver function tests (LFTs) been improved by fibrate use in those with probable NAFLD/NASH but the improvements were related to baseline LFTs; greatest benefit gained by those with highest baseline LFTs. It is possible that this reduction was due to treatment of NAFLD/NASH by the fibrate[92] which would be in keeping with current theories on NAFLD/NASH aetiology. A two or three hit hypothesis for NAFLD/NASH was initially proposed with accumulation of hepatic fat being the "first hit"[93,94]. Oxidative stress, mitochondrial abnormalities and hormonal imbalance (*e.g.*, adiponectin and leptin levels) impairing hepatocyte regeneration and proliferation were considered as possible candidates for the second and third hit[95,96]. Fibrates may have a beneficial effect on fatty acid oxidation (reducing hepatic fat accumulation) and inflammation[95,96]. Thus, improvement in LFTs associated with fibrates may be due to improving these risk factors.

Our work has also confirmed that increases in creatinine concentration is often seen following fibrate use, in line with that described in the FIELD study[63,83], this increase appears to be reversible on discontinuing treatment. We have described the frequency distribution in estimated glomerular filtation rate (eGFR) that may be seen[97]. Clinically this is important as a lower eGFR could lead to withdrawal of other drugs such as metformin, incretins and sodium glucose transporter 2 inhibitors in patients with type 2 diabetes. We also identified the patient group where hypercreatininaemia was more likely: Male gender, lower baseline creatinine concentrations, non-diabetics and greater decrease in TG levels[98].

PARADOXICAL EFFECTS OF FIBRATES

Despite the evidence clearly demonstrating increases in HDL-C caused by statins there have been "paradoxical HDL-C decreases" described. This rare phenomenon also appears to occur in some treated with either a fibrate or a thiazolidinedione (PPARγ agonists). The paradoxical HDL-C decrease was initially reported by Chandler *et al*[99] in 1994; HDL-C was seen to decrease from 0.9 to 0.18 mmol/L following ciprofibrate treatment. A similar paradoxical response in 2 patients was noted when rosiglitazone was added to fenofibrate[100]. In a case series of this phenomenon in 5 patients, we suggested heterogeneity in response following fibrate and rosiglitazone treatment[101]. We also showed that pioglitazone also demonstrated this phenomenon, until then only rosiglitazone had been implicated[102]. Fibrates and glitazones combined with fibrates have been estimated to reduce HDL-C by 0.02% and 1.39% respectively[103]. The pathophysiology of this is unknown but theories include that this is *via* a PPARα based mechanism as HDL-C metabolism is affected by PPARγ activators *via* the PPARα receptor[104].

We investigated this rare phenomenon in 25 patients attending our metabolic clinic; the paradoxical HDL-C decrease was defined by us as a reduction in HDL-C of greater than 50%. This relatively large group of patients with this rare phenomenon enabled us to investigate the

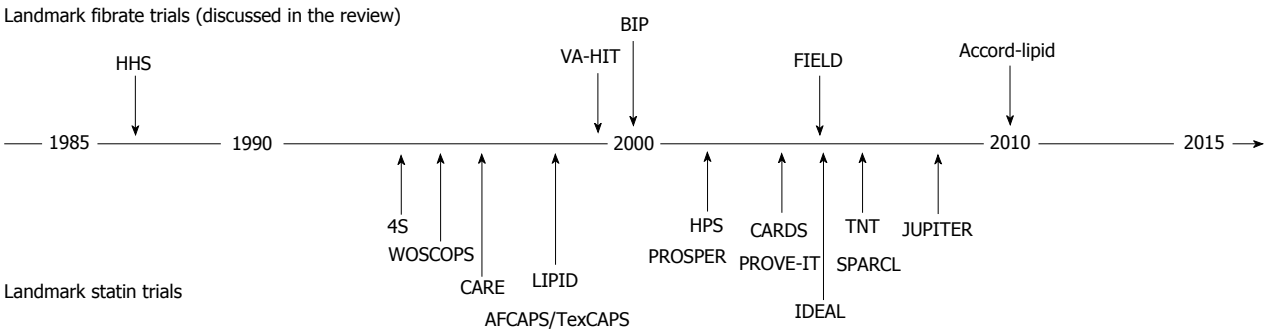

Figure 3 A time line with landmark statin and fibrate randomised control trials (arrows indicate the year of main publication). The fibrate trials are discussed in the review, while the statin trials are only mentioned when relevant. All the statin trials showed that lowering of LDL-C significantly reduced the cardiovascular event chosen as study outcome. 4S: The scandinavian simvastatin survival study; WOSCOPS: West of scotland coronary prevention study; CARE: Cholesterol and recurrent events trial; LIPID: Long-term intervention with pravastatin in ischaemic disease trial; AFCAPS/TexCAPS: Air force/Texas coronary prevention study; HPS: Heart protection study; PROSPER: The prospective study of pravastatin in the elderly at risk; CARDS: Collaborative atorvastatin diabetes study; PROVE-IT: The pravastatin or atorvastatin evaluation and infection therapy trial; IDEAL: The incremental decrease in events through aggressive lipid lowering study; TNT: Treating to new targets trial; SPARCL: The stroke prevention by aggressive reduction in cholesterol levels trial; JUPITER: Justfication for the use of stains in primary prevention: An intervention trial evaluating rosuvastatin trial.

differing presentation patterns[101,102]. These included: (1) the phenomenon observed with all fibrates; (2) effect observed with one fibrate, but not other fibrates; (3) when rosiglitazone (but not pioglitazone) was added to a fibrate; (4) when either rosiglitazone or pioglitazone were added to a fibrate; (5) effect only seen when the dose of fibrates and/or glitazones was increased; and (6) decrease in Apo-A1 - seen in all, except in one patient.

Many questions remain about this interesting group of patients. Most of these, such as whether the CVD risk of these patients is different to those not showing this phenomenon, may remain unanswered due to small numbers. Understanding the mechanisms is problematic as clinical heterogeneity is evident even within this rare group. At this stage we would recommend withdrawal of the offending fibrate, although it is worth trying another fibrate, if fibrate treatment is indicated, albeit with regular measures of HDL-C.

FIBRATES AND CVD: GUIDELINES

The National Institute for Health and Care Excellence (NICE) lipid modification guidelines (CG181) issued in the United Kingdom in 2014 do not recommend routine use of fibrates for primary or secondary prevention, in those with chronic kidney disease or type 1 diabetes[3]. Fibrates may be considered in the context of mixed dyslipidaemia and hypertriglyceridaemia though guidance is not particularly specific, particularly for those with TG between 4.5-9.9 mmol/L. For hypertriglyceridaemia urgent specialist referral, for those with TG > 20 mmol/L in the absence of poorly controlled diabetes and alcohol excess, is recommended. Intermediate TG levels (10-20 mmol/L) should trigger a repeat for confirmation and if patients demonstrate a fasting TG > 10 mmol/L they should also be referred to a specialist. The complexity and variety of various dyslipidaemias is not catered for in this guidance and therefore, we urge clinicians to consider individualised care or specialist referral to make a decision based on the available evidence, pathophysiology and clinical context, which is acknowledged by NICE and recommended in European guidance[3,11]. Therefore fibrates are not currently a main feature of CVD risk management. However we urge clinicians to consider them, particularly in those who may gain the most benefit, *e.g.,* atherogenic dyslipidaemia.

FIBRATES AND CVD: A PERSONAL VIEW

We have well over 20 years of experience in secondary care clinics using all available lipid lowering agents. Our approach to CVD risk reduction is to critically evaluate current evidence and apply it in patient management together with an understanding of the physiology and pathology of atherogenesis. This may be at odds with the current trend which may have led to the NICE guidelines of 2014[3]. At present RCTs dominate the landscape. However, RCTs are selective and real world experience should also play a significant part. We do concur that in most cases of dyslipidaemia statins are the front-line agents. Figure 3 shows a time line with landmark statin and fibrate studies highlighted. The statin trials have all showed significant reductions in the cardiovascular events chosen as outcomes in the respective studies. Each successive trial has added another layer of knowledge to the point that further large scale trials may not be of use. As we have seen previously the understanding of fibrates has travelled in the opposite direction. However, after having considered the overall evidence, our view is that fibrates neatly complement statins (and other LDL-C reducing agents). Their action is on VLDL and HDL, particles which are not significantly affected by statins. Fibrates are very complex compounds with a myriad of actions. At times paradoxical effects are seen which add to the complexity.

We have to reiterate that guidelines are for guidance and education. As practitioners of medicine we have

to combine them with knowledge and understanding of the underlying disorder(s). This is the approach we have adopted and we do use fibrates in patients with hypertriglyceridaemia, the decision reached on a case by case basis. Thus, it was reassuring that the subgroup (metabolic syndrome) outcomes and meta-analyses support our viewpoint. Regarding HDL-C we are not certain as to the role of fibrates. This is mainly as HDL metabolism/cholesterol efflux is not measured as opposed to HDL-C. Our approach will change in the future with further study.

FUTURE DEVELOPMENTS

Other existing TG medications such as omega-3 fatty acids have a less clear evidence base than fibrates in regards to CVD risk reduction. This may be due to lack of specific efficacy or that the benefit is not mediated directly by TG reduction but by other unidentified mechanisms. Further, research is required to answer these questions and also the effects in combination with fibrates.

Development of novel agents that treat hypertriglycerideamia (including genetic hypertriglyceridaemic states) with greater efficacy may clarify the role of TG reduction in CVD risk management. For example gene therapy with lipoprotein lipase replacement may well reduce pancreatitis in those with familial lipoprotein lipase deficiency, however, long term data and larger patient numbers are required to establish their role regards CVD outcomes[105].

Further elucidation, of the role of TG and CVD, may also occur with the introduction of non-HDL in the recent NICE guidance on lipid guidance and CVD risk assessment[3]. This will lead to postprandial hypertriglyceridaemia being represented in CVD risk assessment[3]. Data suggest that postprandial hypertriglyceridaemia is an independent CVD risk factor and that it is non-fasting TG, rather than fasting TG, that provide the main risk[106]. There is evidence that fibrates are useful in ameliorating vascular damage caused by postprandial elevations in TG level by targeting TG metabolism, although the evidence is not conclusive at the current time with robust outcome data lacking[107-109].

CONCLUSION

Clearly the evidence for fibrate use in CVD remains controversial with subgroup and *post hoc* analysis suggesting that PPARα agonism by fibrates in those with low HDL-C and elevated TG levels, the atherogenic dyslipidaemia, could provide additional benefit. However, the blanket use of statins, suggested by guidelines, may contribute to the underlying dyslipidaemia and metabolic derangement being ignored and additional therapies not being offered. Statins should be the front-line agent in our view, except in patients with significantly elevated TG. However, there exists data that suggests that in patients with the atherogenic dyslipidaemia, the dyslipdaemia seen in the metabolic syndrome, fibrates may have a role. This evidence is perhaps submerged by the data collected from statin RCTs. In the United States the prevalence of metabolic syndrome is about 40%[110], therefore, small benefits in this group may have a large impact on the global CVD burden.

Besides CVD, other macrovascular and microvascular complications may be ameliorated by fibrates and therefore a holistic and individualised treatment plan is encouraged. What are required are trials looking at fibrates and statins in relevant groups designed to detect CVD benefits. Work may be aided by the development of high potency PPARα agonists, the assumption being that greater efficacy at lipid reduction and increased cholesterol efflux may translate to greater and therefore universally detectable CVD benefit which would put the current controversy to rest[111].

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REVIEW

Role of vitamin D in diabetes mellitus and chronic kidney disease

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Abstract

Approximately 30%-50% of people are recognized to have low levels of vitamin D, and insufficiency and deficiency of vitamin D are recognized as global health problems worldwide. Although the presence of hypo-vitamin D increases the risk of rickets and fractures, low vitamin D levels are also associated with hypertension, cancer, and cardiovascular disease. In addition, diabetes mellitus (DM) and chronic kidney disease (CKD) are also related to vitamin D levels. Vitamin D deficiency has been linked to onset and progression of DM. Although in patients with DM the relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out, evidence regarding vitamin D levels and DM is contradictory, and well controlled studies are needed. In addition, vitamin D influences the renin-angiotensin system, inflammation, and mineral bone disease, which may be associated with the cause and progression CKD. There is increasing evidence that vitamin D deficiency may be a risk factor for DM and CKD; however, it remains uncertain whether vitamin D deficiency also predisposes to death from DM and CKD. Although at this time, supplementation with vitamin D has not been shown to improve glycemic control or prevent incident DM, clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed. This review focuses on the mechanism of vitamin D insufficiency and deficiency in DM or CKD, and discusses the current evidence regarding supplementation with vitamin D in patients with these diseases.

Key words: Vitamin D; Vitamin D deficiency; Diabetes mellitus; Chronic kidney disease; Cardiovascular disease

Core tip: Vitamin D plays an essential role in diabetes

mellitus (DM) and chronic kidney disease (CKD). The relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out. Vitamin D deficiency has been linked with the renin-angiotensin system and inflammation, which may be associated with the cause and progression CKD. There is increasing evidence that vitamin D deficiency may be a risk factor for DM and CKD. Clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed.

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INTRODUCTION

Diabetes mellitus (DM) and chronic kidney disease (CKD) are common diseases worldwide, and their prevalence continues to increase[1,2]. Vitamin D deficiency is also recognized as a worldwide health problem[3], and is associated with rickets and fracture. In addition, hypovitamin D has recently been considered a responsible factor in the onset and progression of DM and CKD. There has been increasing evidence suggesting that an inverse vitamin D status is prevalent in patients with DM or CKD[4]. Furthermore, supplementation of vitamin D in patients with DM or CKD has been reported in several trials and a meta-analysis[5]. In this review, we provide current clinical data on the mechanism of vitamin D deficiency and the effects of vitamin D on patients with DM or CKD.

VITAMIN D PHYSIOLOGY

Vitamin D is a fat-soluble steroid hormone derived from dietary intake as well as synthesis through the skin *via* exposure to sunlight (Figure 1). Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are produced through solar ultraviolet B radiation (UVB; wavelength 290 to 315 nm). Vitamin D_3 is manufactured from previtamin D_3, which is changed through UVB irradiation from provitamin D_3[6]. Most 25-hydroxyvitamin (25[OH]D) is derived from skin conversion. An alternative source is from dietary intake, mainly from foods of plant or animal origin. In general, animals and fish contain vitamin D_3, and mushrooms contain vitamin D_2[7]. Vitamin D from the skin and diet is either stored in adipose tissue or converted to 25(OH)D in the liver. Vitamin D metabolism requires two hydroxylations to form its active metabolite. The first hydroxylation of vitamin D takes place in the liver where vitamin D is metabolized to 25(OH)D by cytochrome P 2R1 (CYP2R1). 25(OH)D binds to vitamin D-binding protein (DBP) and can flow into the blood in a stable form. 25(OH)D-DBP complex is excreted into the urine and reabsorbed through megalin, a multiligand scavenger receptor in the proximal tubules[8,9], where the complex is converted by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and changed to its active form 1,25-dihydroxyvitamin $(OH)_2D$, although other tissues have 1α-hydroxylase enzymatic activity[10]. CYP27B1 gene expression in the kidney is mediated by various factors. Parathyroid hormone (PTH), hypocalcemia, hypophosphatemia, and calcitonin affect the activation of CYP27B1 and can increase 1,25-$(OH)_2D$ levels. On the other hand, 1,25-$(OH)_2D$ and fibroblast growth factor-23 (FGF-23) inhibit CYP27B1 and can decrease 1,25-$(OH)_2D$ levels[11].

The binding of 1,25$(OH)_2D$ to the vitamin D receptor (VDR) in the nuclear receptor affects gene transcription. In general, 1,25$(OH)_2D$ promotes dietary calcium and phosphorus absorption in the intestine and regulates reabsorption of calcium in the renal tubules. Because VDR is expressed in a variety of organs, such as the heart, liver, blood vessels, and the central nervous system, 25-hydroxyvitamin D-1α-hydroxylase is also expressed in these tissues[12].

It is widely believed that 25(OH)D is the only precursor of 1,25$(OH)_2D$ and does not influence individual tissues. However, recent reports revealed that 25(OH)D has a weak binding capacity for VDR and affects several tissues in the autocrine or paracrine system[13,14]. In addition, extrarenal 1α-hydroxylase enzymatic activity is controlled in different ways that that in renal tubular cells[15].

EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Because 1,25$(OH)_2D$ has a short half-life (approximately 15 h), 1,25$(OH)_2D$ levels are not considered a good indicator of vitamin D levels. As 25(OH)D is more stable in the blood than 1,25$(OH)_2D$, blood concentrations of 25(OH)D are 500 to 1000 times higher than 1,25$(OH)_2D$ concentrations. Therefore, to evaluate vitamin D deficiency and insufficiency, serum 25(OH)D concentrations are considered an adequate biomarker. The United States Institute of Medicine defines vitamin D deficiency as 25(OH)D levels less than 20 ng/mL and greater than 20 ng/mL is sufficient upon evidence related to bone health[16]. Several studies reported that people with 25(OH)D levels less than 20 ng/mL is the risk factor of fracture[17] and have greater subsequent rates of bone loss[18]. On the other hand, the Endocrine Society's guidelines, which are based on patients with endocrine disorders, define vitamin D insufficiency as 25(OH)D levels of 21-29 ng/mL[19,20]. Despite these different definitions, both guidelines agree that vitamin D insufficiency and deficiency are common problems in certain populations.

About 1 billion people worldwide lack vitamin D[21,22]. Vitamin D deficiency and insufficiency are prevalent conditions not only in elderly people but also

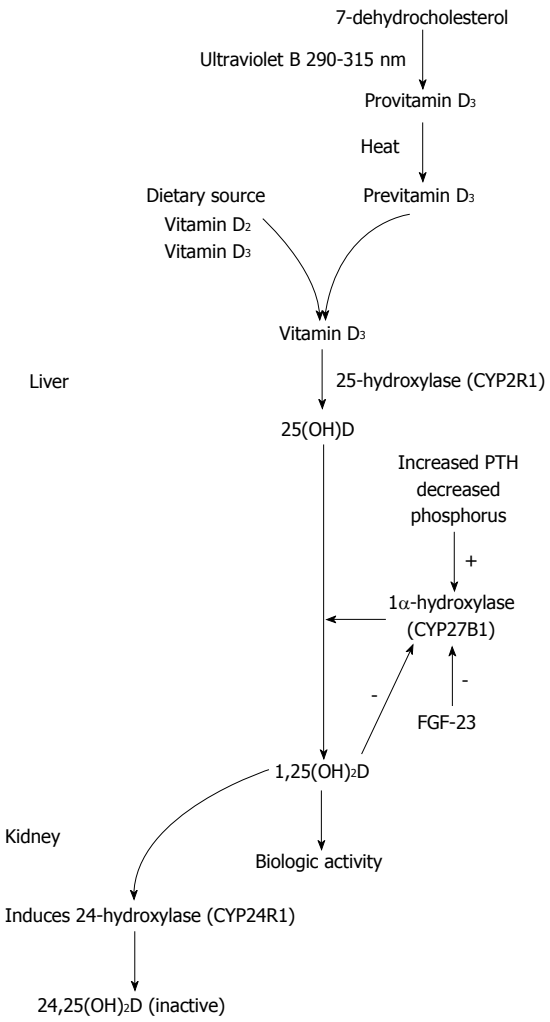

Figure 1 Mechanism of vitamin D synthesis. FGF-23: Fibroblast growth factor-23.

in adolescents[23] and children[24]. One study reported that almost one half of participants had 25(OH)D levels less than 40 nmol/L during the winter and spring[25]. In this study, 7437 people from a British birth cohort study who were 45 years old had 25(OH)D levels measured. Although the prevalence of hypovitamin D, defined as levels below 40 nmol/L, was 15.4% during the spring and summer, the proportion was 46.6% during the winter and autumn. Other studies showed that vitamin D deficiency was especially common in older persons (67-95 years)[26,27], and more than 50% of postmenopausal women taking medication for osteoporosis had 25(OH)D levels below 30 ng/mL[28]. Various factors, including age, sex, location, nutrition status, and physical fitness, affect vitamin D status[29]. In addition, diabetes, renal function, hypoalbuminemia, and albuminuria are also risk factors for vitamin D deficiency[30,31].

Recently, the relationship between 25(OH)D levels and genetic polymorphisms of DBP were reported[32]. It was previously known that 25(OH)D concentrations differed between black Americans and whites[33]. Although it was generally thought that nutritional, environmental, and hormonal factors affected racial differences[34], the detailed mechanisms behind these differences are unknown. Powe *et al*[32] reported that although total 25(OH)D and DBP were lower in black subjects than in white subjects, concentrations of estimated bioavailable 25(OH)D were similar between black and white subjects. In addition, because the affinity of DBP to 25(OH)D differs in the DBP gene polymorphism, genetic polymorphisms of DBP genes (rs7041 and rs4588) provide a likely explanation for racial variations in levels of DBP and 25(OH)D[35]. The combination of rs7041 and rs4588 produces amino acid changes resulting in variant DBPs (Gc1F, Gc1S, and Gc2). The phenotype of Gc1F, which is common in black homozygotes, was associated with the lowest levels of DBP (Gc1F/Gc1F homozygotes). On the other hand, Gc1S, which is common in white subjects, was associated with the highest DBP levels (Gc1S/Gc1S homozygotes). The Gc2/Gc2 homozygotes and Gc1F/Gc1S heterozygotes were associated with intermediate DBP levels. These findings suggest that racial differences in the distribution of DBP and total 25(OH)D are caused by DBP polymorphisms, and low total 25(OH)D levels do not indicate vitamin D deficiency. For purposes of cross-racial evaluations of vitamin D deficiency, it might be appropriate to estimate serum total 25(OH)D concentrations using DBP polymorphisms and DBP.

Associations between vitamin D levels and mortality have been shown by several observational studies[36,37]. Low vitamin D levels have also been shown to be associated with obesity, fractures, and infections[38]. Several observational studies have revealed potential links between low vitamin D levels and cardiovascular disease[39]. It is well known that people who live at high altitudes are at higher risk for hypertension and cardiovascular disease[40,41]. In a study of patients with hypertension who were exposed to UVB radiation three times a week for 3 mo, 25(OH)D concentrations increased by about 180%, and blood pressure became normal[42]. A prospective, nested, case-control study of 1484 women without hypertension and with low 25(OH)D levels showed that women with lower 25(OH)D levels had a higher rate of incident hypertension than controls. Low 25(OH)D concentrations have been shown to be inversely related to developing hypertension[43]. A recent Mendelian randomization study of vitamin D status and blood pressure concluded that increased plasma concentrations of 25(OH)D might reduce the risk for hypertension[44]. Cardiovascular disease such as coronary arterial disease[45], myocardial infarction[46], heart failure[47], and stroke[48] are also associated with vitamin D deficiency. However, a recent study showed that high levels of 25(OH)D were also associated with cardiovascular disease mortality[49]. This prospective, observational, cohort study analyzed 247574 citizens from Denmark and showed that a 25(OH)D level below 12.5 nmol/L was associated with a higher risk for mortality [hazard ratio (HR) = 1.59] compared with the reference range (50-75 nmol/L); however, those with

levels higher than 125 nmol/L had the highest mortality risk (HR = 1.95). There is a possibility that maintaining adequate vitamin D levels is essential for human health.

As mentioned above, vitamin D status and cardiovascular disease are strongly associated. Animal models offer several mechanisms to explain this association. Activation of the renin-angiotensin-aldosterone system (RAAS) has been seen in VDR knockout mice[50], and vitamin D has been shown to regulate the nuclear factor kappa beta pathway in renal failure model mice[51]. In vascular endothelial cells, transcription of nitric oxide synthase has been shown to be inhibited by vitamin D in mice[52]. In addition, vitamin D has been shown to activate the Keap1-Nrf pathway, which opposes oxidative stress, in renal failure model mice[53].

VITAMIN D AND DM

Type 1 DM

Type 1 DM is caused by a complex autoimmune destruction of pancreatic islet β-cells, leading to absolute insulin deficiency. The autoimmune nature of type 1 DM has been clarified with the detection of autoantibodies against islet β-cells and their infiltration by T cells, B cells, and macrophages[54]. Vitamin D has been shown to have immunomodulatory properties as well. Many immunomodulatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease have been reported to be associated with vitamin D deficiency[55,56]. Type 1 DM is also said to be related to vitamin D deficiency[57]. As VDR are expressed in human T and B lymphocytes, vitamin D is thought to modify the Th1/Th2 cytokine profile[58]. In addition, vitamin D is also thought to be associated with the immune system *via* its inhibition of lymphocyte proliferation[59]. Non-obese diabetic (NOD) mice with vitamin D deficiency showed an increased incidence and severity of diabetes[60]. Using $1,25(OH)_2D$ reduced the manifestation of diabetes in NOD mice by decreasing the number of effector T cells[61,62]. Another study reported that $1,25(OH)_2D$ also counteracted cytokine-induced expression of Fas, which regulates cell death in human islet cells[63].

The relationship between sunlight exposure and the incidence of type 1 DM has been reported[64]. One study showed that providing vitamin D supplements to infants in North Europe, where daylight hours are shorter than in other countries, decreased the risk for new-onset type 1 DM[65]. Although children suspected of having rickets during the study period had a relative risk (RR) of 3.0 (1.0-9.0) for type 1 DM, children who had taken 2000 IU vitamin D daily had a RR = 0.22 (0.05-0.89). Some studies were designed to clarify the effect of vitamin D on the preservation of β-cell function after the onset of type 1 DM[66]. Two studies found no significant effects of administration on vitamin D in protecting β-cell function[67,68]. However, another study reported significant effects of vitamin D administration on maintaining β-cell function after the development of type 1 DM. Thirty-eight patients with new-onset type 1 DM were randomly assigned to receive daily oral therapy with cholecalciferol, 2000 IU, or placebo[69]. The cumulative incidence of progression to undetectable ($\leqslant$ 0.1 ng/mL) fasting C-peptide and stimulated C-peptide levels was lower in the cholecalciferol group than in the placebo group. In another study, alfacalcidol (0.25 μg/d) preserved β-cell function in children with newly diagnosed type 1 DM[70]. Further studies are needed to clarify whether the administration of 25(OH)D or $1,25(OH)_2D$ can inhibit the onset of type 1 DM.

Type 2 DM

As VDRs in pancreatic β-cells play an important role in the progression of type 2 DM[71], vitamin D deficiency is related to insulin secretion, insulin resistance, and β-cell dysfunction in the pancreas[72] (Figure 2). The secretion of pancreatic insulin is inhibited by vitamin D deficiency in the diabetic animal model[73,74]. Administration of vitamin D restores glucose-stimulated insulin secretion and promotes β-cell survival by modulating the generation and effects of cytokines[75,76]. Insulin secretion is also influenced by calcium concentration and flux through the β-cells[77]. Vitamin D regulates the function of calbindin, a systolic calcium-binding protein found in pancreatic β-cells, and acts as a modulator of depolarization-stimulated insulin secretion *via* regulation of intracellular calcium[78]. PTH, which has its concentration regulated by vitamin D, is associated with insulin synthesis and secretion in the pancreas[79].

Insulin sensitivity is also associated with vitamin D. By stimulating the expression of insulin receptors, vitamin D regulates insulin sensitivity[80,81]. In addition, vitamin D enhances insulin sensitivity by promoting the expression of peroxisome proliferator-activated receptor (PPAR) delta, which is a widely expressed member of the PPAR family of nuclear receptor fatty acid sensors and regulates fatty acids in skeletal muscle and adipose tissue[82]. Intracellular calcium is a key factor of peripheral insulin resistance *via* an impaired signal transduction pathway leading to decreased glucose transporter activity[83,84].

The indirect effect of vitamin D is exerted by regulating calcium flux through the cell membrane and intracellular calcium. While low vitamin D induces secondary hyperparathyroidism, increased PTH levels are also associated with diabetes. A recent observational study of 494 women undergoing serial metabolic characterization revealed that hypovitamin D levels with increased PTH levels were an independent predictor of β-cell dysfunction, insulin resistance, and glycemia[85]. Vitamin D affects insulin resistance through the RAAS. One animal study demonstrated that vitamin D negatively regulated expression of renin genes in a mice model[86]. Furthermore, low levels of $1,25(OH)_2D$ increased renal renin production and activated the RAAS system in an animal model[87]. Finally, angiotensin Ⅱ inhibited the action of insulin in vascular and skeletal muscle tissues, leading to impaired glucose uptake[88].

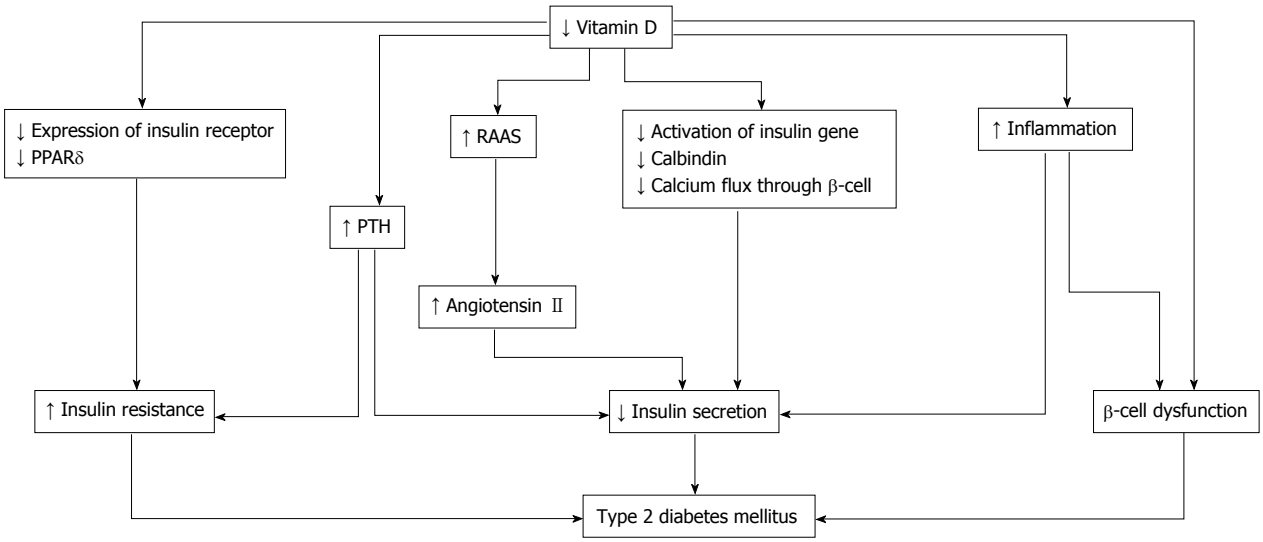

Figure 2 Putative scheme of effect of vitamin D on type 2 diabetes mellitus. PPAR: Peroxisome proliferator-activated receptor; PTH: Parathyroid hormone; RAAS: Renin-angiotensin-aldosterone system.

Systemic inflammation has an important role in insulin resistance and cardiovascular events in patients with type 2 DM[89]. As β-cells in the pancreas are affected *via* cytokine-induced apoptosis, high levels of inflammation cause worsening glycemic control. Vitamin D could decrease the effects of systemic inflammation and protect against β-cell cytokine-induced apoptosis by directly modulating the expression and activity of cytokines, as has been shown in animal models[90]. In patients with type 2 DM**,** incubation of isolated monocytes with 1,25(OH)$_2$D decreased the expression of inflammatory cytokines affecting insulin resistance, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α[91].

A prospective cohort study designed in the United Kingdom showed that baseline 25(OH)D concentrations in patients without diabetes were inversely related with the risk for hyperglycemia and insulin resistance at 10 years of follow-up visits[92]. Moreover, a similar study reported that low 25(OH)D levels were a risk factor for type 2 DM[93]. This prospective, cohort study was conducted over 29 years among 9841 subjects without diabetes. Lower vitamin D levels were a risk factor for incident type 2 DM. However, a recent Mendelian randomization approach study found that low 25(OH)D levels were not genetically associated with the risk for type 2 DM[94]. This result suggests that the association between 25(OH)D concentrations and type 2 DM is not causal. A meta-analysis of 16 studies reported that the odds ratio for type 2 DM was 1.5 (1.33-1.70) for the bottom *vs* top quartile of 25(OH)D levels[95]. Numerous randomized controlled studies have investigated whether vitamin D supplementation influences glycemic homeostasis[96,97]. As described above, vitamin D is thought to improve insulin resistance and promote insulin secretion. Therefore, clinical trials often use outcomes such as homeostasis model assessment of insulin resistance, fasting plasma glucose levels, and hemoglobin A1c levels. Some clinical trials have assessed the combined effects of vitamin D and calcium supplementation on glucose homeostasis of patients with diabetes[98,99] and without diabetes[100]. These studies suggest that vitamin D plus adequate calcium levels might be needed for an improvement in glycemic status. However, a recent meta-analysis concluded that vitamin D supplementation given to address concerns with glycemic control and insulin resistance in patients with diabetes is not recommended, although the doses of vitamin D supplementation may not have been optimal; almost all of the included trials used vitamin D doses of at least 2000 IU/d[101]. Because most trials focused on glycemic status and insulin resistance over short durations (12 mo or less), we should await the results of ongoing trials with longer follow-up periods to provide new evidence regarding the potential role of vitamin D supplementation in type 2 DM[102].

One study was designed to examine the protective effect of vitamin D against the development of type 2 DM[103]. A total of 2447 older people (mean age, 77 years) were allocated to 800 IU daily vitamin D$_3$ and 1000 mg calcium both, or placebo for 24-62 mo. Vitamin D in combination with calcium was not able to prevent the development of diabetes or an increase in the need for medication in patients with diabetes. The Women's Health Initiative Calcium/Vitamin D Study, a randomized, placebo-controlled trial of 33951 postmenopausal women, followed participants receiving 1000 mg elemental calcium plus 400 IU of vitamin D$_3$ daily, or placebo for 7 years. Calcium plus vitamin D$_3$ supplementation did not reduce the risk for developing diabetes over 7 years[104]. These results suggest that vitamin D supplementation at doses of 400 to 800 IU/d, with or without calcium, does not prevent new-onset type 2 DM.

Although at this time, supplementation with vitamin D has not been shown to improve glycemic control or

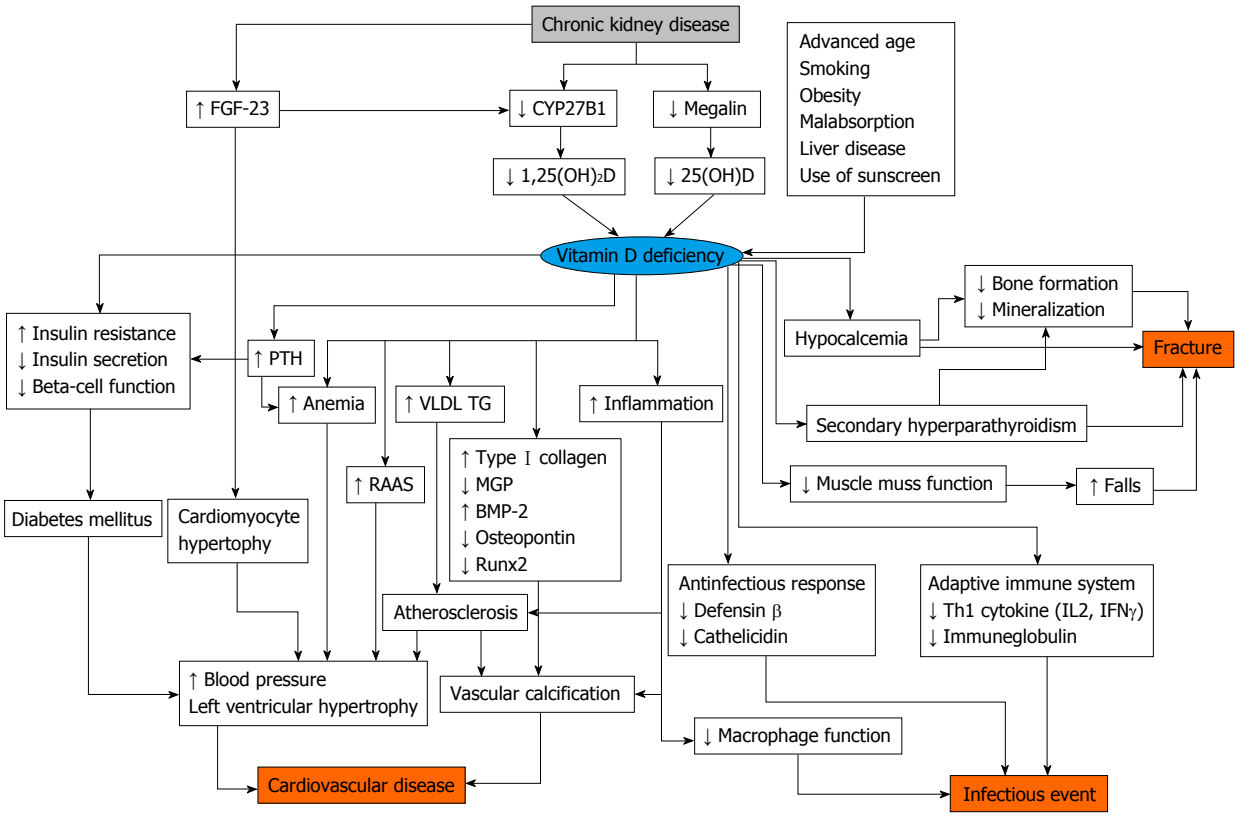

Figure 3 Vitamin D deficiency and cardiovascular disease. FGF-23: Fibroblast growth factor-23; PPAR: Peroxisome proliferator-activated receptor; PTH: Parathyroid hormone; RAAS: Renin-angiotensin-aldosterone system; VLDL: Very low density lipoprotein; TG: Triglycerides; IL: Interleukin; IFN: Interferon; MGP: Matrix gla protein; BMP: Bone morphogenetic protein.

prevent incident type 2 DM, clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed. In addition, it is important that future studies of vitamin D use primary outcomes, such as all-cause mortality and cardiovascular disease, as endpoints.

VITAMIN D AND CKD

One study revealed that paricalcitol diminished residual albuminuria in patients with diabetic nephropathy[105]. In this study, patients were randomly assigned (1:1:1) to receive placebo, 1 μg/d paricalcitol, or 2 μg/d paricalcitol for 24 wk to investigate the effect on mean urinary albumin-to-creatinine ratio (UACR). Patients receiving 2 μg paricalcitol showed a nearly sustained reduction in UACR, ranging from -18% to -28% (P = 0.014 *vs* placebo). However, few trials have used a vitamin D receptor antagonist (VDRA) for patients with diabetes, and none has a sufficient number of patients or follow-up period. The effect of vitamin D_3 and VDRA on hard outcomes, such as progression of diabetes, cardiovascular disease, and all-cause mortality, requires larger and longer-term trials.

Some studies indicate that 1,25(OH)$_2$D levels decrease in patients with CKD[106]. There are the several theories about the pathogenesis of vitamin D deficiency in CKD. Megalin, which is present in endocytic receptors in proximal tubule cells, is involved in the reabsorption of DBP from glomerular ultrafiltrates[107]. In addition, megalin also mediates the subsequent intracellular conversion of 25(OH)D to its active form. As kidney function declines, megalin expression in the proximal tubule decreases[108]. Megalin function is also attenuated with reduced kidney function, because of damages from low molecular weight proteinuria. The activity of CYP27B1 is also associated with decreasing kidney function[109]. As FGF-23 reduces expression of cotransporters NaPi-Ⅱa and NaPi-Ⅱc, of the brush border in the proximal tubules, these mechanisms inhibit phosphorus absorption and CYP27B1 activity.

In addition to the decline of 1,25(OH)$_2$D levels, 25(OH)D levels also decrease in patients with CKD. There are the several plausible mechanisms that explain the decreases in 25(OH)D. The complex of 25(OH)D and DBP leaks with proteinuria. Uptake of 25(OH)D decreases due to down-regulation of megalin levels. One study showed that 25(OH)D concentrations in patients with CKD were low[110]. The prevalence of vitamin D deficiency is 35% among about 4000 patients with CKD in the United States[111].

There is some evidence that vitamin D status is associated with poor clinical outcomes in patients with CKD[112] (Figure 3). Low 25(OH)D levels are associated with all-cause mortality and cardiovascular disease in patients with CKD[113]. The risk for end stage renal disease is higher in patients with low vitamin D status. Among patients undergoing hemodialysis and peritoneal

dialysis, low 25(OH)D levels are also associated with cardiovascular disease[114].

There is some evidence regarding restitution of vitamin D in patients with CKD[115,116] and as well as in patients undergoing dialysis [117,118]. As previously described, patients with kidney failure usually have insufficient 1,25(OH)$_2$D levels, and a VDRA is used for these patients. One study revealed that paricalcitol diminished albuminuria in patients with diabetic nephropathy[105]. In the VITAL study, which was designed to compare the effectiveness between paricalcitol and placebo, the paricalcitol group showed a decreased UACR of -16% compared with placebo[105]. However, as of yet, no other studies have investigated the effectiveness of vitamin D supplementation for protection of kidney function; thus, future studies are needed. Another study showed that paricalcitol led to decreases in levels of brain natriuretic peptide (BNP) in patients with CKD[119]. On the other hand, a recent study reported that treatment with paricalcitol did not improve left ventricular mass and function in patients with CKD[120]. There is controversial evidence regarding the role of VDRA to cardiovascular disease and surrogate makers. It is thought that as 1,25(OH)$_2$D inhibits activation of the RAAS, it leads to organ protection[121]. In addition, there is some evidence regarding VDRAs in patients undergoing hemodialysis. A retrospective cohort study showed that VDRA users had a lower mortality rate than non-VDRA users[122]. However, the Dialysis Outcomes and Practice Patterns Study revealed that taking vitamin D agents did not improve clinical outcome in patients undergoing dialysis. In addition, a recent study reported that pharmacological doses of alfacalcidol were associated with accelerated progression of aortic stiffness in patients undergoing hemodialysis[123]. To date, various discussions have taken place regarding the use of VDRA in patients undergoing dialysis, but adequate clinical studies are needed before any recommendations can be made.

According to the Kidney Disease Improving Global Outcomes guidelines, 25(OH)D levels should be determined in patients with CKD stage 3-5, and if levels are low, physicians should consider vitamin D supplementation[124]. Low 25(OH)D levels are associated with all-cause mortality and cardiovascular disease in patients with CKD as well as in patients undergoing dialysis[125]. Another study showed that among these patient groups, those with low levels of 25(OH)D and high levels of FGF-23 have worse outcomes[38]. However, there is not sufficient evidence regarding vitamin D supplementation for patients with CKD and those undergoing dialysis[126]. Although studies have reported that cholecalciferol decreases albuminuria[127,128] and improves PTH levels[129] in patients with CKD, there is no study with set clinical outcomes such as all-cause mortality or cardiovascular disease. In patients undergoing dialysis, cholecalciferol decreases BNP levels and reduces left ventricular hypertrophy[130]. As VDRAs increase calcium and phosphorus levels in patients undergoing dialysis, it is usually recommended that physicians only need to monitor calcium and phosphorus levels when using a VDRA[131]. On the other hand, vitamin D$_3$, such as cholecalciferol, does not increase calcium and phosphorus levels[132,133]. As with patients with CKD, there is no evidence with hard endpoints regarding the use of vitamin D$_3$ supplementation in patients undergoing hemodialysis.

CONCLUSION

Emerging evidence is accumulating on the important role of vitamin D in the pathogenesis of diabetes and CKD. Many prospective studies have shown associations between vitamin D status and chronic disease, including diabetes and CKD. However, there are contradictory findings regarding whether restitution of normal vitamin D levels modifies the occurrence or clinical course of these diseases. Although there is a concern that vitamin D may be a surrogate marker for poor health status, further well-designed clinical trials are needed in this area.

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MINIREVIEWS

Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management

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Abstract

Patients with diabetes mellitus (DM) frequently develop electrolyte disorders, including hyperkalemia. The most important causal factor of chronic hyperkalemia in patients with diabetes is the syndrome of hyporeninemic hypoaldosteronism (HH), but other conditions may also contribute. Moreover, as hyperkalemia is related to the blockage of the renin-angiotensin-aldosterone system (RAAS) and HH is most common among patients with mild to moderate renal insufficiency due to diabetic nephropathy (DN), the proper evaluation and management of these patients is quite complex. Despite its obvious relationship with diabetic nephropathy, HH is also related to other microvascular complications, such as DN, particularly the autonomic type. To confirm the diagnosis, plasma aldosterone concentration and the levels of renin and cortisol are measured when the RAAS is activated. In addition, synthetic mineralocorticoid and/or diuretics are used for the treatment of this syndrome. However, few studies on the implications of HH in the treatment of patients with DM have been conducted in recent years, and therefore little, if any, progress has been made. This comprehensive review highlights the findings regarding the epidemiology, diagnosis, and management recommendations for HH in patients with DM to clarify the diagnosis of this clinical condition, which is often neglected, and to assist in the improvement of patient care.

Key words: Hyporeninemic; Diabetes; Hyperkalemia; Renal tubular acidosis; Hypoaldosteronism

Core tip: Hyporeninemic hypoaldosteronism is the most significant cause of hyperkalemia in patients with diabetes mellitus. In order to help physicians, diabetologists, and endocrinologists in proper management of this condition, this review will focus on the current available evidence, highlighting the consequences of this condition for the treatment of arterial hypertension and proteinuria in these patients.

Sousa AGP, Cabral JVS, El-Feghaly WB, Sousa LS, Nunes AB. Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management. *World J Diabetes* 2016; 7(5): 101-111 Available from: URL: http://www.wjgnet.com/1948-9358/full/v7/i5/101.htm DOI: http://dx.doi.org/10.4239/wjd.v7.i5.101

INTRODUCTION

Hyperkalemia, usually defined by a potassium concentration greater than 5.5 or 6.0 mEq/L (mmol/L)[1], is a common clinical condition and is potentially life-threatening due to the risk of ileus paralysis and fatal arrhythmias[2]. Among the various causes of hyperkalemia, hypoaldosteronism should be considered in any patient with persistent hyperkalemia for which there is no clear cause, such as renal failure, the use of potassium supplements or a potassium-sparing diuretic. The causes of hypoaldosteronism include both acquired (secondary mineralocorticoid deficiency) and, less often, inherited disorders (primary mineralocorticoid deficiency), which can affect adrenal aldosterone synthesis or renal (and maybe adrenal) renin release. The most common secondary mineralocorticoid deficiency cause is hyporeninemic hypoaldosteronism (HH), including cases related to diabetes mellitus (DM), pharmacologic inhibition of angiotensin Ⅱ, the use of potassium-sparing diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) or calcineurin inhibitors[3]. Primary hypoaldosteronism can be the result of acquired or congenital errors in renal juxtaglomerular function, angiotensin generation or activity, or aldosterone synthesis. Secondary hypoaldosteronism (pseudohypoaldosteronism), in contrast, occurs as a consequence of mutations in genes that may adversely affect aldosterone-mediated electrolyte homeostasis[4].

For decades, it has been known that there is a relationship between the metabolism of glucose and potassium; the lack of insulin predisposes one to hyperkalemia, exogenous insulin lowers serum potassium, and potassium deficiency interferes with insulin release, leading to glucose intolerance[5]. In addition, hyperkalemia occurs more frequently in patients with DM than in the general population[6]. Various mechanisms are involved in the development of hyperkalemia in patients with DM, for example hyperosmolality, insulin deficiency or resistance, HH, potassium-sparing drugs, and raised glucagon concentrations[2]. HH is related to a secondary mineralocorticoid deficiency, leads to hyperkalemia accompanied by urinary salt wasting[7] and is commonly seen in association with diabetic nephropathy (DN). HH normally occurs when there is some underlying renal pathology causing volume expansion[8].

A few years ago, a series of publications addressed the close relationship between HH and DM in case reports and studies on physiology and applied pathophysiology. However, most of these studies were published before the spread of the use of medications that interfere with the renin-angiotensin-aldosterone system (RAAS), such as inhibitors of the angiotensinogen-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Currently, few studies have reported on the implications of the diagnosis of HH in patients with DM, the concerns of a diagnosis of HH for the management of antihypertensive medications (ACEIs and ARBs) and the natural history of nephropathy in patients with DM. The objective of this review is to highlight the pathophysiology and diagnosis of HH in patients with DM, as well as the consequences of this condition for the treatment of arterial hypertension (AH) and proteinuria in these patients.

PATHOPHYSIOLOGY

For the purpose of maintaining homeostasis, the urinary excretion of potassium is typically equal to the quantity ingested minus the quantity excreted in the feces[6]. In normal individuals, most of the potassium filtered at the glomerulus is reabsorbed in the proximal tubule and in the ascending limb of Henle's loop, and most of the potassium excreted in the urine is that secreted by the distal convoluted tubule and the cortical collecting tubule (CCT)[7]. Consequently, potassium secretion in the cortical collecting duct is the major determinant of urinary potassium excretion[6]. However, the amount of potassium finally excreted in the urine is typically less than the amount secreted by earlier segments because there is a considerable quantity of potassium reabsorbed at the outer medullary collecting duct[3]. Potassium enters the tubular cell in exchange for sodium by the action of the Na-K ATPase located at the basolateral membrane, an active transport mechanism that moves three sodium ions out of the cell while simultaneously carrying two potassium ions into the cell. This process is able to maintain a high potassium and a low sodium concentration in the cell. Aldosterone stimulates Na-K ATPase activity directly and increases luminal membrane permeability to sodium. It also increases the permeability of the luminal membrane to potassium[6]. Aldosterone thus plays a major role in regulating the renal excretion of potassium. The action of aldosterone is to increase the number of open sodium channels in the luminal membrane of the principal cells in the CCT, leading to increased sodium reabsorption. The subsequent elimination of sodium from the tubular

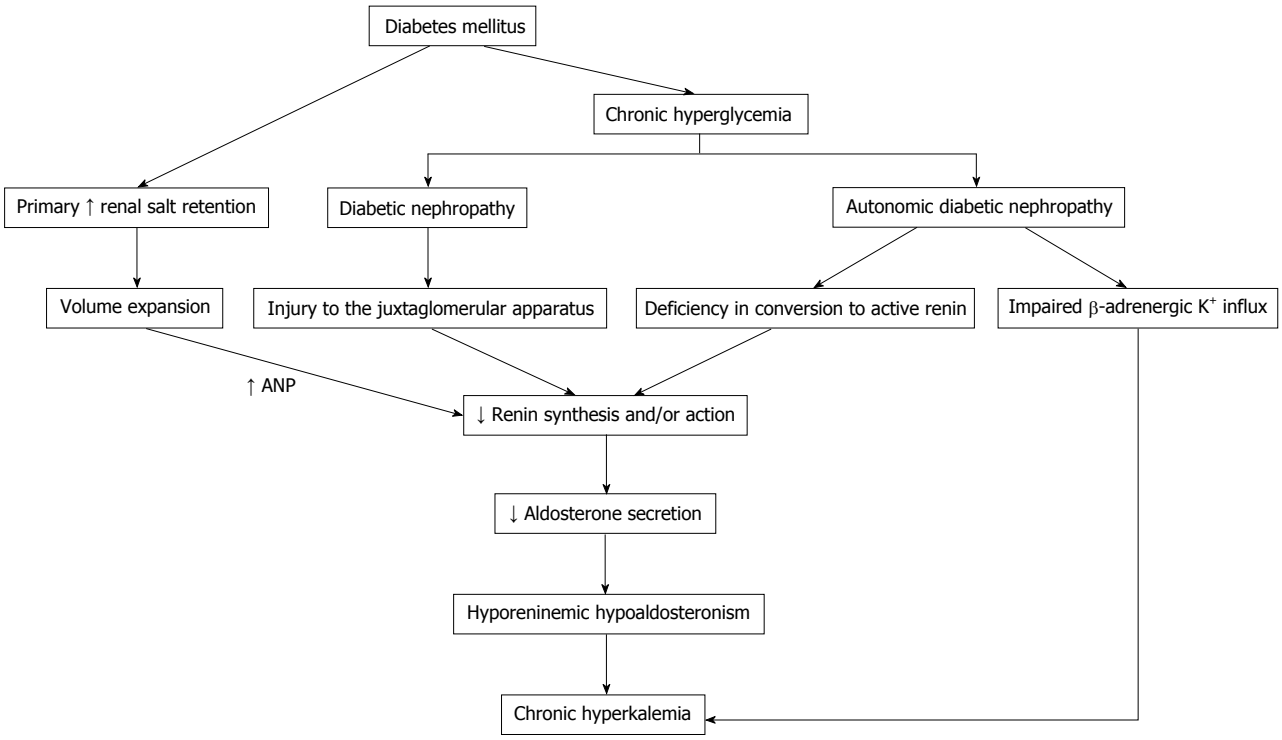

Figure 1 Pathophysiology of hyporeninemic hypoaldosteronism related to diabetes mellitus. ANP: Atrial natriuretic peptide; K^+: Potassium.

fluid makes the lumen electronegative, thereby creating an electrical gradient that stimulates the secretion of potassium into the lumen through potassium channels in the luminal membrane[7].

HH is a syndrome that is related to a reduction in the production of aldosterone from the adrenal gland and in the release of renin from the juxtaglomerular cells. A reduced renin release results in a decreased systemic and intra-adrenal angiotensin Ⅱ (AngⅡ) production, which contributes to the decline in aldosterone secretion[9]. AngⅡ is a cofactor, along with potassium, in aldosterone synthesis by the adrenal gland. The production of renin occurs in the kidney by the juxtaglomerular cells and is stimulated primarily by the reduction in intravascular volume. Therefore, the RAAS plays a key role in blood pressure regulation[7]. HH is most common among patients with mild to moderate renal insufficiency due to DN or chronic interstitial nephritis[10]. As seen in Figure 1, the reduction in renin release in patients with DM may be secondary to[10]: (1) injury to the juxtaglomerular apparatus (such as an afferent arteriolar hyalinization); (2) defects in the stimulation factors or suppressed plasma renin activity (PRA) because of the deficiency in conversion of prorenin (big renin) to active renin; (3) autonomic dysfunction (as part of the autonomic diabetic neuropathy); or (4) an primary increase in renal salt retention with volume expansion, which suppresses renin synthesis (paradoxically, if compared to individuals without DM). The volume expansion leads to the suppression of renin release because of an increase in release of atrial natriuretic peptide, thus contributing to HH[11]. It is important to emphasize that any condition in which the renin-angiotensin-aldosterone axis is interrupted can potentially produce type Ⅳ renal tubular acidosis (RTA); therefore, type Ⅳ RTA and HH are often considered synonymous. Renal tubular damage may cause inadequate renin production and release, adrenal dysfunction may lead to inadequate aldosterone production, and the principal cells of the CCT may not respond normally to aldosterone. In addition, atrophy of the juxtaglomerular apparatus may be present, and this may be more prevalent among diabetic patients. This atrophy is related to autonomic neuropathy[12], chronic hyperkalemia and volume expansion[11]. In addition, any combination of these factors may cause HH or type IV RTA. Indeed, all of these factors (or any combination of them) may be present in some patients[13].

Because there is a reduced secretion of potassium, which can lead to chronic hyperkalemia, the resulting hyperkalemia impairs $NH4^+$ production in the collecting duct. This leads to impaired generation of acid for excretion and metabolic acidosis[14], usually hyperchloremic metabolic acidosis, due to the deficiency in potassium and hydrogen secretion[15]. The degree of acidosis varies and may be related to the underlying chronic kidney disease (CKD). In type Ⅰ (*i.e.*, distal) RTA, the defect is in proton secretion with a resulting high urine pH (> 5.3), whereas in type Ⅳ RTA, the primary defect is in ammoniagenesis. This defect, albeit significant, still permits elaboration of acidic (pH < 5.3) urine. Hyperkalemia inhibits renal ammoniagenesis in several ways that involve the direct effects of one on the other: Modulation of ion transport by aldosterone, lowering of ammonia formation, and defective medullary ammonium handling. Furthermore, it may produce

acidosis by shifting protons from inside the cells to the extracellular space as homeostatic mechanisms attempt to buffer potassium by intracellular uptake[2].

EPIDEMIOLOGY

HH predominantly occurs in patients 50 to 70 years of age with DN and/or chronic tubulointerstitial disease who have mild to moderate kidney failure[16]. It is more frequent among women. Therefore, patients with these characteristics should be monitored[17]. Other common clinical conditions associated with HH include various forms of interstitial disease, such as amyloid, monoclonal gammopathies and the interstitial nephritis associated with NSAIDs in particular[2,18-20]. In addition, there is a close relationship between diabetes and hyperkalemia. Insulin deficiency, kidney disease, HH, and use of medications such as ACEIs and ARBs that increase the risk of hyperkalemia are mechanisms involved in this relationship[21]. Therefore, hyperkalemia can be observed in type 1 DM patients due to their insulin deficiency and ketone-prone condition, as well as in type 2 DM patients, in whom an association has been found between serum potassium concentration and incidence of hyperkalemia and insulin resistance (estimated by the homeostasis model assessment)[21]. In addition, serum potassium concentration is likely to be more increased in patients with poorly controlled type 2 DM with insulin resistance than in those without DM[22]. Clinicians must also be aware that hyperkalemia in patients with type 1 DM may be due to concurrent adrenal insufficiency in the case of autoimmune polyglandular syndrome[23]. Specifically about HH, in many cases, particularly DN, hypoaldosteronism and low renin levels are present. In previous studies, about half of the subjects with HH were found to be diabetics[10]. Moreover, although HH usually occurs with persistent high potassium levels, some cases of HH are not accompanied by hyperkalemia despite suppression of renin and aldosterone levels. A previous study assessed the renin-aldosterone axis in 13 normokalemic patients with DM and creatinine clearances of < 40 mL/min and showed that approximately 92.3% of them had HH[24]. However, no recent studies have assessed the prevalence of HH in individuals with DM, particularly among those with normal renal function and/or without hyperkalemia. Similarly, the incidence of hyperkalemia in patients with HH could not be found. However, such studies are difficult to conduct because HH is often underdiagnosed and habitually only manifests when the patient is challenged by excess dietary potassium or by exposure to medications; furthermore, HH improves upon the removal of the exacerbating agents. In addition, it is worth noting that these older studies were conducted when the use of ACEIs and ARBs was not widespread. Recently, only a few studies have been conducted with moot methodology to determine the current incidence and prevalence of HH among populations that include patients using these medications. One recent study[25] evaluated the prevalence and role of type Ⅳ RTA in the development of significant hyperkalemia in patients admitted to a hospital for over 1 year and found significant hyperkalemia (> 6.0 mEq/L) in 3.8% of hospital admissions. Type Ⅳ RTA was diagnosed in 42% of these patients, of whom 71% had pre-existing renal insufficiency due to DN or tubulointerstitial nephritis. In the same study, patients with type Ⅳ RTA more frequently had a history of DM (50% *vs* 24%, $P = 0.07$) and were more likely to have pre-existing kidney failure (71% *vs* 38%, $P < 0.05$). No significant difference in the use of ACEIs, ARBs, NSAIDs, or another potassium-sparing diuretics was found between the groups with or without type Ⅳ RTA[25]. In another pharmacovigilance study, life-threatening hyperkalemia was found to be related to polypharmacy (use of more than 5 drugs), age (greater than 74 years), gender (female) and glomerular filtration rate (GFR) < 60 mL/min[26].

CLINICAL FEATURES AND DIAGNOSIS

In patients with persistent hyperkalemia with no obvious cause (such as renal failure, the use of potassium supplements or a potassium-sparing diuretic), the diagnosis of hypoaldosteronism should be considered[9]. These patients typically have elevated potassium serum levels disproportional to their renal function and potassium intake. Actually, HH accounts for most cases of unexplained hyperkalemia in patients in whom GFR and potassium intake would not be expected to result in hyperkalemia[2]. Regarding its clinical manifestation, most patients with HH are asymptomatic and have mild to moderate hyperkalemia. However, patients with HH may have significant hyperkalemia with no manifestations for long periods of time and may occasionally be identified in routine laboratory tests[6]. Conversely, an acute event (renal dysfunction or salt restriction) or medication (such as ACEIs, ARBs, potassium-sparing diuretics or heparin) may sometimes precipitate hyperkalemia in a patient whose disease has not been recognized because his or her plasma potassium has not exceeded the normal range. In those cases, acute hyperkalemia can disturb excitable tissues and provide different manifestations depending on the potassium serum level. Nausea, muscle weakness, paresthesias and fasciculations may occur and could progress to paralysis in severe cases. The progressive effects on the heart can be seen in the electrocardiogram (ECG), namely the peaking of T waves, ST-segment depression, widening of the PR interval, widening of the QRS interval, loss of the P wave, and development of a sine-wave pattern[3], and may even culminate in ventricular fibrillation. Generally, with acute onset of hyperkalemia, ECG changes appear at a serum potassium level of 6-7 mEq/L (6-7 mmol/L). However, with chronic hyperkalemia, the ECG may remain normal up to a concentration of 8-9 mEq/L (8-9 mmol/L)[3]. Despite these findings, a retrospective study revealed a poor correlation between serum potassium concentrations and cardiac manifestations[27].

Furthermore, hypoaldosteronism has been related with mild hyperchloremic metabolic acidosis. Metabolic acidosis is primarily the result of impaired renal ammoniagenesis caused by hyperkalemia (type Ⅳ RTA), reduced aldosterone levels, and reduced distal delivery of sodium. The acidosis is hyperchloremic because the renal insufficiency is mild and the retention of uremic anions is slight. Patients' urinary pH is characteristically acidic because impaired ammoniagenesis reduces the buffering capacity of urine; occasionally, patients cannot acidify urine because of an associated distal tubular defect in hydrogen ion secretion[6]. Chronic hyperkalemia, *per se*, is usually asymptomatic, but chronic acidosis contributes to long-term morbid conditions, including bone demineralization[28]. Hyponatremia is uncommon in HH because there is no hypovolemia-induced stimulation to release antidiuretic hormone (ADH) and the plasma cortisol level, a tonic inhibitor of ADH release, is normal. Otherwise, when hyponatremia is present, other disorders such as primary adrenal insufficiency should be suspected[9].

Regarding the diagnosis of HH, it is important to remember that middle-aged or elderly patients with chronic hyperkalemia, diabetes, and/or with renal insufficiency are at risk. However, patients with DM at any age and metabolic conditions can be at risk. A study performed some years ago described a 31-year-old man with insulin-dependent DM and previous normal renal function who presented with symptomatic hyperkalemia and reversible impairment of renal function when treated with enalapril[29]. Before performing laboratory and dynamic tests to confirm HH, patients should be questioned about increased dietary potassium intake (including fruit juices and herbal preparations, such as noni), cell lysis (rhabdomyolysis), and the use of medications that interfere with potassium levels, such as ACEIs, ARBs, NSAIDs, beta-blockers, calcineurin inhibitor (cyclosporine, for example) and heparin, as well as human immunodeficiency virus (HIV) infection[6]. Patients with HIV are at risk for adrenal insufficiency, which may present as hyperkalemia. Nevertheless, the adrenal defect is sometimes selective for mineralocorticoid production. Furthermore, trimethoprim, a drug commonly used in chemoprophylaxis regimens for patients with AIDS, may impair tubular potassium excretion and may cause hyperkalemia[3]. In women, the use of some oral contraceptives should be evaluated because the progestin drospirenone retains mineralocorticoid blocking effects similar to those seen with spironolactone[30]. Other rarer diseases that can also cause nephropathy and HH may need to be excluded, for example, multiple myeloma, amyloidosis, systemic lupus erythematosus, and genetic disorders (pseudohypoaldosteronism)[7]. Some researchers also recommend excluding alcohol consumption, hemolysis, rhabdomyolysis, and/or metabolic acidosis[2]. In addition, as revealed before, clinicians must also be aware that hyperkalemia in patients with type 1 DM may be due to concurrent adrenal insufficiency in the case of autoimmune polyglandular syndrome.

As previously mentioned, HH should be suspected in cases of unexplained chronic hyperkalemia in patients in whom GFR and potassium intake would likely not result in hyperkalemia. After exclusion of those possible causes, to confirm and to perform a differential diagnosis of hypoaldosteronism, it is recommended that the PRA, serum aldosterone, and serum cortisol should be measured (Figure 2). Some authors[9] recommend that these tests should be performed after the administration of a loop diuretic (furosemide) or after three hours in the upright position, which increases renin and aldosterone release in normal individuals. This ensures activation of the RAAS and the reliability of the findings, especially in the HH context. Hyperkalemia in patients with chronic kidney failure that is well short of end-stage (stage Ⅴ) is typically characterized by plasma aldosterone levels that are inappropriately low for the degree of hyperkalemia[13]. Therefore, the authors of this article believe that, after excluding other causes, the existence of significant hyperkalemia (potassium levels > 5.5-6.0 mEq/L) accompanied by low or inappropriately normal aldosterone levels is indicative of hypoaldosteronism. In addition, HH is characterized by a low (or low normal) PRA and commonly normal serum cortisol[9]. Conversely, in the absence of significant hyperkalemia, it is important to ensure activation of the RAAS by the furosemide or upright test. These tests have commonly been used to differentiate between aldosterone-producing adenoma and idiopathic hyperaldosteronism in cases of primary aldosteronism[31], but they have recently been used increasingly less often for this purpose[32]. In brief, after a minimum of 1 wk on a 90 mmol/d sodium diet and in a potassium-replete state, the furosemide test can be performed after administration of a dose of 2 mg/kg of body weight orally at 06:00. The dose is then repeated 6 h later at 12:00 (if systolic blood pressure is ⩾ 120 mmHg without orthostatic hypotension). At 1800 (6 h after the second dose of furosemide), a blood sample to measure PRA and aldosterone, sodium, and potassium concentrations is obtained after 5 min in the sitting position[31]. Other authors have used a combined test (upright position with administration of 60 mg furosemide)[33] for clinical research purposes in particular. In cases of primary adrenal insufficiency, both serum aldosterone and cortisol concentrations are typically low and PRA high. Ultimately, unlike primary hyperaldosteronism, there are no cutoffs for the diagnosis of HH. Consequently, reference values of laboratory tests are commonly used. Considering the lack of recent data concerning the diagnosis of HH, the impact of ACEI and ARB use is unknown. These medications are known to alter the aldosterone:PRA ratio by increasing the PRA[34], potentially reducing aldosterone levels. Therefore, there may be doubt regarding whether these medications interfere with the diagnosis of HH. In the absence of specific studies, the authors of this article believe that the suspension of ACEIs and ARBs is not essential to establish a diagnosis of HH. If a patient using these

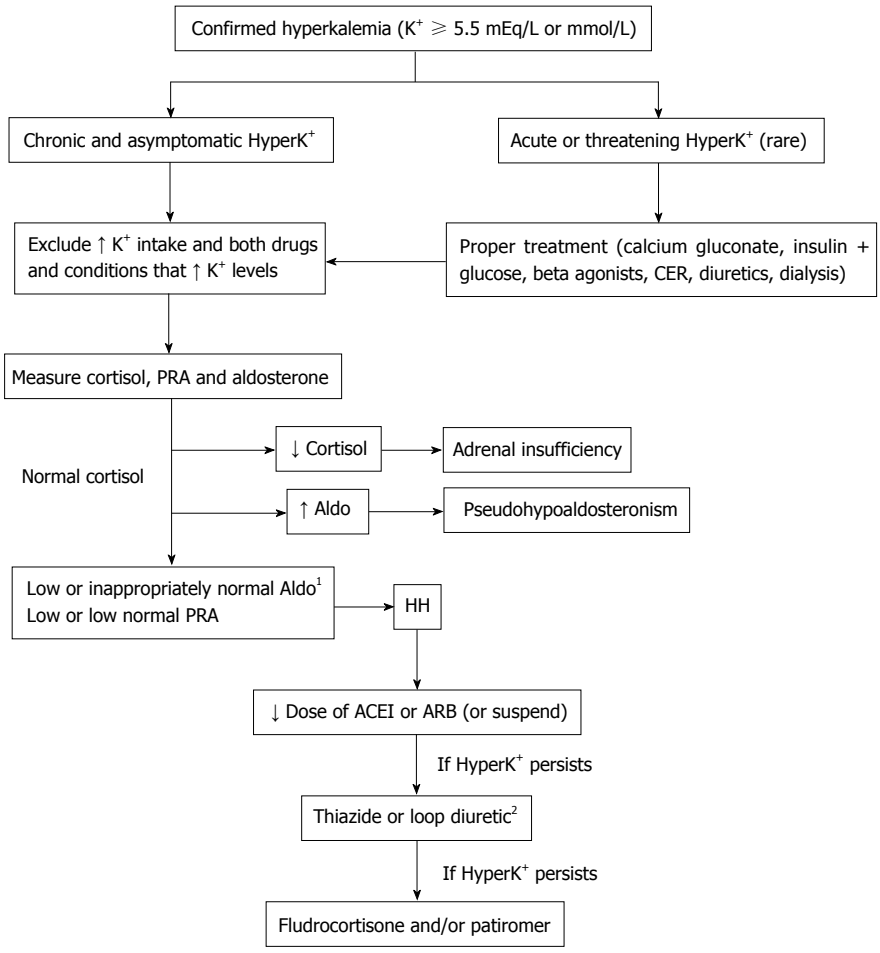

Figure 2 Diagnosis and management of hyporeninemic hypoaldosteronism related to diabetes mellitus. [1]In any cases, it might be necessary to activate the renin-angiotensin-aldosterone system (using a loop diuretic or the upright position); [2]After using diuretics, the use of ACEIs or ARBs should be restarted (if suspended). ACEIs: Angiotensinogen-converting enzyme inhibitors; Aldo: Aldosterone; ARBs: Angiotensin receptor blockers; CER: Calcium exchange resins; HyperK^+: Hyperkalemia; K^+: Potassium; PRA: Plasma renin activity; HH: Hyporeninemic hypoaldosteronism.

drugs develops hyperkalemia without impaired renal function and has low or inappropriately normal aldosterone and PRA levels, the most likely diagnosis is HH. However, if the suspension of drugs is necessary (either because of continuing concerns about the diagnosis or because of hyperkalemia), aldosterone and PRA should be repeated. Potassium-sparing diuretics (such as spironolactone and eplerenone), however, must be suspended before hormonal laboratory evaluation. Finally, further studies are clearly needed to clarify these issues.

RELATION TO OTHER DIABETIC MICROVASCULAR COMPLICATIONS

As previously stated, HH is most often found in patients with DN. It is therefore more likely to diagnose HH in patients with other diabetic microvascular complications. Considering the limited number of recent studies, few (if any) advances in the understanding of this issue have been obtained. Obviously, a key point in the explanation of these findings is hyporeninemia. Its association with DN is at least in part related to the damage to the juxtaglomerular apparatus and problems in the conversion of prorenin to active renin in diabetic patients[16]. The most comprehensive hypothesis accounting for the hyporeninemia is the associated renal disease-associated destruction of renin-producing cells (JG cells) or impaired function of the juxtaglomerular apparatus. However, the pathological findings of the juxtaglomerular apparatus in HH are limited in number and are likely nonspecific (they are found in essential hypertension, for instance)[10]. In addition, previous studies have suggested that impaired conversion of prorenin to active renin may cause a clinically significant reduction of PRA[35]. Nevertheless, the molecular mechanisms that explain how renal dysfunctions affect this conversion remain uncertain. A study designed to clarify the cause of selective HH divided 118 normokalemic patients based on presence or absence of diabetic neuropathy and/or nephropathy, and the authors observed that the development of abnormalities was associated with diabetic neuropathy and/or nephropathy[33]. According to a different study[36], autonomic neuropathy may be more relevant in HH than nephropathy: In patients with type 2 DM and autonomic neuropathy, levels of PRA were lower and inactive renin levels were higher, regardless of proteinuria

and GFR. In addition, a Japanese study on the postural test and neuropathic diabetes showed that autonomic dysfunction was a major factor in impairing the processing of prorenin to active renin in diabetic patients and that severe autonomic dysfunction may impair the biosynthesis of prorenin in patients with HH[37]. In fact, autonomic neuropathy is known to result in impaired beta2-mediated influx of potassium into cells[38]. In addition, the stimulation of beta-adrenergic receptors induces renin release[39]; autonomic neuropathy with consequent sympathetic insufficiency might therefore lead to an impairment of renin production in patients with DM[10]. Theoretically, the suppression of PRA that results from sympathetic dysfunction should lead to a reduction in blood pressure; however, most reported patients with HH have AH[10]. Thus, these data reveal a significant association between other diabetic microvascular complications and HH, but no single pathophysiological aspect is able to accurately explain the findings observed related to DM-HH. It is most likely that there is a combination of mechanisms that together explain HH within the spectrum of microvascular diabetic complications.

IMPLICATIONS FOR THE MANAGEMENT OF AH AND PROTEINURIA

Patients with DM commonly use ACEIs and ARBs when they have concurrent hypertension and/or DN or for cardiovascular protection[40]. Despite the decrease in PRA in DN[34], the RAAS is fundamental in DN pathogenesis; there is an increased production of Ang Ⅱ secondary to stimulation by hyperglycemia and advanced glycation end products. Ang Ⅱ promotes an increase in intraglomerular pressure and adrenal aldosterone production. In addition, prorenin and aldosterone contribute to renal fibrosis[34]. Therefore, ACEIs and ARBs are essential for nephroprotection. However, one of the main adverse effects of these medications is hyperkalemia. The patients at the highest risk for hyperkalemia include those with either diabetes or those with impaired renal function in whom a defect in the excretion of renal potassium may already exist[41], including patients with HH. The development of hyperkalemia as a direct or indirect consequence of decreased aldosterone concentrations is typically observed when aldosterone concentrations have already decreased prior to the administration of drugs[41]. DN is the most common cause of HH, ranging from 43% to 63% of cases[9,42]. In addition, the risk of hyperkalemia increases with the progression of DM as a result of insulin deficiency, by limiting the body's ability to shift potassium into cells[41]. ACEIs and ARBs impair the urinary excretion of potassium by inhibiting the stimulatory effect of Ang Ⅱ on aldosterone secretion in the adrenal gland. ACEIs act by blocking the formation of Ang Ⅱ, whereas ARBs prevent Ang Ⅱ from binding to its adrenal receptor, both systemically and perhaps within the adrenal zona glomerulosa[43]. However, while the effects of these medications in patients with HH can be inferred, they have not been evaluated through specific clinical studies.

The role of RAAS inhibition in postponing the progression of DN by using ACEIs or ARBs has been well established in multiple controlled trials; these medications are thus the drugs of choice in the treatment of hypertension and/or proteinuria in patients with DM[41]. In adult patients with diabetes and kidney disease, ACEIs and ARBs have been the most effective strategies in preventing progression to end-stage kidney disease[44]. Unfortunately, the true prevalence of HH in patients with DM, especially those with DN, is not known. However, given the vast prevalence of DM worldwide, it is thought that there are many patients with HH (even with normal levels of potassium) using ACEIs or ARBs. The large clinical trials that evaluated the efficacy of ACEIs, ARBs, and direct renin inhibitors on the natural history of DN did not perform post hoc analyses regarding the status of the RAAS (baseline levels of aldosterone and PRA, for example). HH has been suggested to be nephroprotective on its own, as it leads to lower levels of aldosterone and PRA[45]. Thus, one might suggest that the use of medications that interfere with the RAAS would have a modest to no effect on the progression of DN and would only increase the risk of hyperkalemia. However, these issues have not been specifically evaluated and are therefore only suppositions. In the absence of contrary evidence, the authors still believe that ACEIs and ARBs can be used in patients with HH and may even have clinical benefits, since their potassium levels do not present an obstacle and are closely monitored. In fact, the systematic monitoring of potassium levels in patients using RAAS blockers prevents cases of severe hyperkalemia. A study found that patients who received potassium monitoring were 50% less likely to experience a hyperkalemia-associated adverse event [adjusted relative risk of 0.50 (95%CI: 0.37-0.66)] compared to patients without monitoring. In patients with CKD, the adjusted relative risk was even lower at 0.29 (95%CI: 0.18-0.46)[46].

Given the underlying pathophysiology, there was hope that dual RAAS blockade could reduce the progression of DN even further[34]. The potential benefit of this dual blockade has been tested in three large randomized clinical trials, and unfortunately, their results demonstrated a lack of benefit with regard to renal or cardiovascular outcomes in diabetic patients[47-49]. In contrast, a recent meta-analysis found that the progression to end-stage renal disease was significantly less likely after combined treatment with an ARB and an ACEI[44]. However, one of the main safety concerns with more intensive RAAS blockade is hyperkalemia. Thus, careful monitoring of potassium in CKD patients in whom a mineralocorticoid receptor blocker is to be used in combination with an ACEI or ARB is of utmost importance, especially if the patient also has diabetes. While precaution may suggest that this combination should be avoided, it is widely used, especially in cases

of heart failure. Prior studies have shown that the risk factors for hyperkalemia with the use of RAAS blockers include older age, lower GFR, higher baseline potassium levels, and the use of more than one medication that interferes with potassium excretion[50]. In fact, dual RAAS blockade has been shown to increase the risk of hyperkalemia and acute kidney injury. New agents for the treatment of hyperkalemia may increase the feasibility of dual blockade of RAAS; however, further research is still needed[34]. Nevertheless, withholding or withdrawing drugs that block the RAAS on the basis of impaired kidney function or on diagnosis of HH alone may potentially deprive many patients of the cardiovascular benefit they would receive; instead, there are numerous steps that can be taken to minimize the risk of hyperkalemia[3,41]. The initial approach should be to estimate the GFR and the potassium levels to assess the specific risk of hyperkalemia as well as to review the patient's medications profile. Drugs that can impair renal potassium excretion[41,51] should be discontinued. It is important to inquire specifically about the use of over-the-counter NSAIDs and herbal remedies, as herbs can be a hidden source of intake potassium. A low-potassium diet should then be prescribed with specific counseling against the use of potassium-containing salt substitutes. Next, therapy with a low dose of ACEIs or ARBs should be initiated. It is essential to monitor patients' potassium levels within 1 wk after initiating therapy or after increasing dosage[52]. If potassium levels remain normal, the dose of the drug can be titrated upwards. If potassium is higher than 5.5 mEq/L (5.5 mmol/L) despite the steps described above, ACEIs and ARBs may need to be avoided[41,51,52]. When albuminuria and proteinuria occur in DN, RAAS inhibitors should be used aggressively. However, the antiproteinuric effects of ACEIs and ARBs can be observed soon after starting treatment and may decrease the effectiveness throughout the treatment[40,53]. In addition, when an ARB is combined with an ACEI or direct renin inhibitor (such as aliskiren), there has been no evidence of clinical efficacy and adverse reactions have in fact been increased[40]. Despite the fact that ACEIs and ARBs are key drugs for the treatment of DM nephropathy, new treatment strategies are needed to achieve improved effectiveness. Finally, studies evaluating the efficacy and safety of medications in the treatment of hypertension and albuminuria in patients with HH are highly needed.

MANAGEMENT OF HYPERKALEMIA IN PATIENTS WITH HH

The incidence of hyperkalemia is higher in diabetic patients than in the general population[52], and the most common causal factor of chronic hyperkalemia in patients with diabetes is the reduced tubular secretion of potassium due to HH. The development of overt hyperkalemia is most common in patients with other risk factors that further impair the efficiency of potassium excretion, such as renal insufficiency, volume depletion, or the use of medications that interfere through the deterioration of intravascular volume contraction[2]. Indeed, worsening of renal function and hyperkalemia may occur in patients who are using the novel sodium glucose cotransporter 2 inhibitors, particularly those predisposed to hyperkalemia due to impaired renal function, medications, or other medical conditions[54].

There are no recognized recommendations or guidelines regarding when to initiate hyperkalemia treatment, but it is usually necessary to treat hyperkalemia because of the potential clinical manifestations in excitable tissue and the risk of progression to respiratory failure and fatal arrhythmias[3]. A summary of the management of hyperkalemia in patients with DM is presented in Figure 2. In cases of rapid elevation, very high potassium levels, and in life-threatening conditions, emergency treatment should be promptly initiated. Hyperkalemia must be acutely treated to counter its cardiac effects, using calcium gluconate or chloride to decrease the membrane excitability of the cardiac cells and reverse the locking depolarization caused by hyperkalemia. Drugs that provide potassium redistribution between the intra and extracellular fluid should be used. Insulin shifts the potassium into the cell, and the recommended dose is 10 units of regular insulin intravenously together with 50 mL of 50% glucose to prevent hypoglycemia in patients with glycemia below 200-250 mg/dL. Beta agonists, such as salbutamol, are also used to redistribute the potassium and to act synergistically with insulin. The recommended dose is 10-20 mg of nebulized salbutamol in 4 mL of saline solution for 10 min. For potassium removal, calcium exchange resins, diuretics and/or dialysis can be used. The use of bicarbonate infusion should be restricted to patients with associated metabolic acidosis and when it is non-gap metabolic acidosis[27,30]. In addition, the most widely used calcium exchange resin is sodium polystyrene sulfonate. As its effect is slow and there is a potential risk of intestinal injury, it is recommended that the use of this medication be restricted to the acute management of hyperkalemia only and when dialysis is not available or indicated[32]; it must not be used chronically.

In patients with HH in particular, the use of medications that affect the RAAS should be reassessed. In cases of hyperkalemia (serum potassium concentration up to 5.5 mEq/L or mmol/L) in patients with HH using ACEIs, dose reduction may be initially attempted[3]. In some cases, potassium concentration will improve, allowing the patient to remain on the renin-angiotensin blocker, although at a lower dose. ARBs and direct renin inhibitors should be used with the same caution. It is important to remember to recommend a low potassium diet and to avoid the use of NSAIDs, including selective cyclooxygenase-2 inhibitors[41]. Some years ago, a case of selective HH triggered by the use of NSAID was reported[55]. Dual RAAS blockade must be avoided (combinations of ACEIs and ARBs or direct renin inhibitors).

However, the use of aldosterone antagonists (spironolactone or eplerenone) is relatively common. If indicated, the dose of spironolactone should not exceed 25 mg daily when used with an ACEI or ARB, and this combination should be avoided when the GFR is < 30 mL/min. Patients with HH and decompensated diabetes (with significant hyperglycemia, particularly if there is concomitant loss of weight) have an additional increased risk of hyperkalemia; insulin deficiency contributes to both a low serum aldosterone concentration and to an increased concentration of extracellular potassium. In addition to the risk associated with insulin deficiency, hyperglycemia creates a differential osmolality, resulting in a hypertonic extracellular fluid. Consequently, water and ions, as potassium, are attracted to the extracellular fluid. In these patients, the use of insulin for the treatment of hyperglycemia may be recommended[3]. If these actions do not have the expected result and the risk benefit profile is in favor of maintaining the RAAS blockade, the use of fludrocortisone or diuretics can be attempted. Fludrocortisone is a potent mineralocorticoid that promotes increased reabsorption of sodium and loss of potassium from renal distal tubules[9]. While being administered, it is necessary to monitor the concentration of serum sodium and potassium because of the potential risk of hypokalemia and hypokalemic alkalosis[20,31,52]. The typical dose of fludrocortisone required to normalize the serum potassium is usually higher than the dose in primary adrenal insufficiency (0.05 to 0.2 mg daily). Nevertheless, the authors recommend starting with 0.1 to 0.2 mg once a day and increasing the dosage based on potassium levels and signs of hypervolemia. However, fludrocortisone is not widely used; patients with HH often have hypertension and/or edema (heart failure, for instance) and thus should either use fludrocortisone with caution or not use it at all because of its effect on plasma volume expansion. In those cases, hyperkalemia can be treated with low potassium ingestion and drugs that eliminate potassium, such as diuretics[33,35], preferably thiazide or loop ones, because of their efficiency in reducing hyperkalemia[41]. In patients with a GFR < 30 mL/min, a loop diuretic is ideal, as thiazide diuretics are less effective[52]. Alternatively, other authors have initially chosen to suspend the use of ARBs and start diuretics to first control potassium levels and then restart RAAS blockade successfully[56]. However, the use of loop diuretics may lead to the deterioration of renal function because of intravascular volume depletion[20]. If challenges in managing hyperkalemia persist, it is recommended to discontinue medications that act on the RAAS[41]; however, new agents are being evaluated in the treatment of hyperkalemia. Sodium zirconium cyclosilicate, a selective cation exchanger, was tested in a multicenter study and led to a significant reduction in potassium levels at 48 h (approximately 0.5 to 0.7 mEq/L)[57]. However, the most promising drug to date is patiromer, a non-absorbed potassium binder, which has been tested in patients with hyperkalemia and with use of RAAS blockers. In a multicenter study, patiromer was able to significantly reduce the level of potassium by approximately 1 mEq/L (mmol/L) in hyperkalemic patients using ACEIs or ARBs[58].

CONCLUSION

In clinical practice, it is common for patients with DM to present with hyperkalemia, especially if they are monitored for electrolytes. The literature states that the main cause of hyperkalemia in those patients, particularly those who already have diabetic microvascular complications (such as autonomic neuropathy), is HH. However, the recent literature on this topic is quite limited. Despite its pathophysiological importance, the diagnosis of HH is actually difficult to make because of the high frequency of concomitant comorbidities as well as the use of different medications and clinical variability. Clinically, HH is most often found in patients with DN, and the patients typically have asymptomatic, mild to moderate hyperkalemia. The prevalence of HH in the general diabetic population remains unclear, but it is believed to be underdiagnosed by physicians, including diabetologists. ACEIs and ARBs may precipitate hyperkalemia in a patient whose disease has not been recognized and increase the risk of severe hyperkalemia in patients with previously mild hyperkalemia. Although ACEIs and ARBs are considered to be essential for nephroprotection and are key drugs in the treatment of hypertension and DN, new treatment strategies are needed to achieve better effectiveness and control of potassium imbalances. Therefore, preventive actions should be routinely taken when treating such patients, including the proper evaluation of patients with initial borderline hyperkalemia to detect HH and the monitoring of patient potassium levels after initiating or modifying medications that block the RAAS. Undoubtedly, further studies are required to clarify critical issues regarding the syndrome of HH.

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