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INVITED REVIEW

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Lessons learned from the FinnDiane Study: Epidemiology and metabolic risk factors for diabetic kidney disease in type 1 diabetes

Fanny Jansson Sigfrids[1,2,3] | **Raija Lithovius**[1,2,3] | **Per-Henrik Groop**[1,2,3,4,5] | **Lena M. Thorn**[1,2,3,6]

[1]Folkhälsan Research Center, Helsinki, Finland

[2]Research Program for Clinical and Molecular Metabolism, University of Helsinki, Helsinki, Finland

[3]Department of Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[4]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

[5]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

[6]Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Correspondence
Lena M. Thorn, Folkhälsan Research Center, Helsinki 00029, Finland.
Email: lena.thorn@helsinki.fi

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Abstract

Aims: Across its operational span of more than 25 years, the observational, nationwide, multicentre Finnish Diabetic Nephropathy (FinnDiane) Study has aimed to unravel mechanisms underlying diabetic kidney disease, with a special focus on its metabolic risk factors. We sought to compile key findings relating to this topic and to offer a current perspective on the natural course of diabetic kidney disease among individuals with type 1 diabetes.

Methods: In this narrative review, articles relevant to the subject published by the FinnDiane Study were identified and summarized together with work published by others, when relevant.

Results: The FinnDiane Study has underscored the significance of dysglycaemia and insulin resistance, increased visceral fat mass, hypertension and dyslipidaemia—particularly high triglycerides and remnant cholesterol—as risk factors for diabetic kidney disease. Factors like abdominal obesity seem to influence the early stages of the disease, while the presence of the metabolic syndrome becomes implicated at later stages. Epidemiological reports have revealed that after an initial decline, the cumulative incidence of albuminuria plateaued post-1980s, with the progression rate to kidney failure remaining high. Fortunately, 23% of the FinnDiane cohort regressed to less advanced stages of albuminuria, improving their overall prognosis.

Conclusion: A substantial burden of albuminuria associated with type 1 diabetes persists, and therefore, novel kidney-protecting therapies are highly awaited. In addition, given that metabolic factors influence the progression of diabetic kidney disease both in its early and advanced stages, emphasis should be placed on ensuring that their treatment targets are met.

KEYWORDS

albuminuria, diabetic kidney disease, dyslipidaemia, hypertension, insulin resistance, metabolic syndrome, type 1 diabetes

1 | INTRODUCTION

In 1997, the observational Finnish Diabetic Nephropathy (FinnDiane) Study was established with the goal to understand why one-third of individuals with type 1 diabetes develop diabetic kidney disease. The scope has later expanded to cover the other microvascular and macrovascular complications of diabetes as well. Starting as a small-scale pilot project with the goal of recruiting a few hundred individuals, the FinnDiane Study has evolved over the years into one of the largest well-characterized cohorts of individuals with type 1 diabetes, now encompassing nearly 9000 participants from across the country. Despite not being a population-based study by strict definitions, the distribution of study participants mirrors that of the population in Finland (Figure 1). Therefore, the study can be considered as highly representative of the entire population with type 1 diabetes in the country with the highest incidence rate of type 1 diabetes globally.[1]

The characterization of thousands of study participants has been made possible through the efforts of physicians and diabetes nurses at the 78 involved centres across Finland. The cornerstone of the characterization and data collection process lies in the study's clinical visit. Here, data are meticulously collected via comprehensive questionnaires and extensive clinical examinations, as summarized in Figure 1. In addition to the baseline examinations of new participants joining the study, the follow-up has consistently been updated by re-examining participants at the local study centre in Helsinki since the longitudinal phase of the FinnDiane Study began in 2003. Currently, 36% of the participants have attended at least one follow-up visit, with some individuals having been re-examined up to five times throughout their involvement in the study. Additional follow-up data are acquired from national registries and medical records, encompassing serial laboratory measurements for HbA_{1c} and lipids, among others (Figure 1).

Over its more than 25-year span, one line of research by the FinnDiane Study has focused on identifying risk factors for diabetic kidney disease, with a particular emphasis on metabolic determinants. Central to this research have been hyperglycaemia, insulin resistance, abdominal obesity and dyslipidaemia—not to forget hypertension, which serves as both a cause and a consequence of diabetic kidney disease. Importantly, these factors are crucial elements in both primary and secondary prevention strategies for tackling diabetic kidney disease.

This review summarizes key findings from the extensive research by the FinnDiane Study and others in the field of metabolic risk factors for diabetic kidney disease associated with type 1 diabetes. Additionally, we recap the most recent insights into the epidemiology and natural history of this long-term complication, as depicted by the FinnDiane study group.

What's new?

- The burden of diabetic kidney disease in type 1 diabetes remains high and unchanged, with one-third still developing albuminuria.
- The metabolic syndrome is a frequent finding in type 1 diabetes, especially among those with concomitant kidney disease. Its presence is a predictor of future kidney failure.
- Abdominal obesity, as depicted by a waist-height ratio ≥0.5, is associated with new-onset albuminuria.
- The presence of dyslipidaemia increases in parallel with the worsening of diabetic kidney disease. Elevated triglycerides and remnant cholesterol are associated with its progression.
- Several abnormal blood pressure patterns may indicate future kidney complications, even before any clinical symptoms appear.

2 | EPIDEMIOLOGY

2.1 | The incidence and progression of diabetic kidney disease

The early documentation of the epidemiology of kidney disease in type 1 diabetes, published in the first years of the 1980s and including individuals with diabetes onset during the first half of the 20th century, showed that 25%–35% develop proteinuria after 25 years and 35%–45% after 40 years of disease duration.[2,3] Subsequent studies produced varying estimates, but many were limited in scope, often based on small, single-centre populations, which made them less representative of the broader population with type 1 diabetes.[4] There has also been a notable omission of temporal trends in most studies, and the representation of individuals with diabetes onset in the 1990s or later has been infrequent.[4]

Addressing these significant knowledge gaps, researchers from the FinnDiane study group presented an updated perspective on the natural history of diabetic kidney disease in 2022.[5] These findings stem from a population-based cohort of 1500 individuals diagnosed with diabetes between 1970 and 1999 in Finland. This cohort, selected through a stratified random sampling method across three diagnosis periods (1970–79, 1980–89 and 1990–99), represented 14.4% of the complete sampling frame.

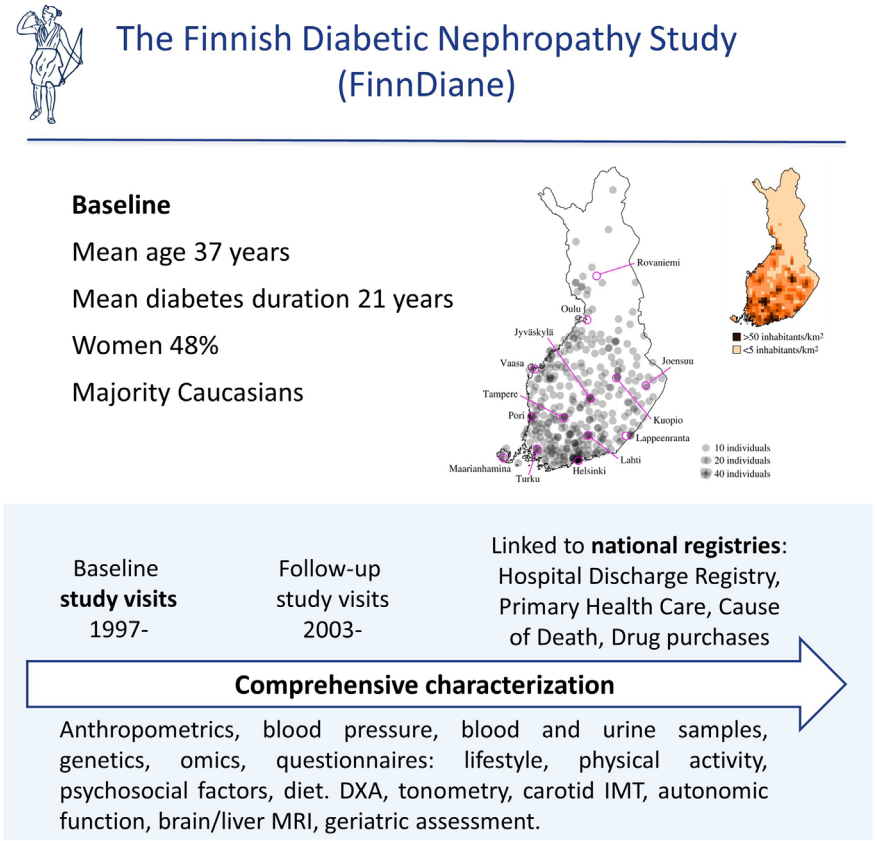

FIGURE 1 A visual summary of the Finnish Diabetic Nephropathy (FinnDiane) Study, its main baseline characteristics, as well as participant characterization. DXA, dual-energy X-ray absorptiometry; IMT, intima-media thickness; MRI, magnetic resonance imaging.

The study unveiled a noteworthy trend in the cumulative incidence of severe albuminuria over time. While there was an initial halving in cumulative incidence after the 1970s, the decline eventually reached a plateau, with no further reduction noted. Consequently, the 25-year cumulative incidence of severe albuminuria for individuals diagnosed in the 1990s stood at 10.8%. The trend for moderate albuminuria (formerly microalbuminuria) followed this pattern, with no difference registered between the 1980s and 1990s diagnosis cohorts (25-year cumulative incidence 29.8% and 30.7% respectively).[5]

The study further identified changes in the diabetes duration-specific incidence rate pattern over time. While the incidence rate of severe albuminuria peaked at 15–19 years (25.8 cases per 1000 person-years) in individuals with diabetes onset in 1970–79, this peak had flattened out in later diagnosis cohorts. Instead, in the later diagnosis cohorts combined (1980–99), the incidence rate rose steadily during the first 15 years since the diabetes onset but levelled out after that, remaining stable throughout the follow-up period at an average incidence rate of 10.2 cases per 1000 person-years. Due to this shift in the incidence rate pattern, the incidence rate was 2.27-fold compared to the earlier diagnosis cohort at 25–29 years of diabetes duration. This prompts the question of whether contemporary treatment methodologies delay rather than truly prevent the development of diabetic kidney disease.[5]

Alarming numbers on the progression of albuminuria were also revealed: within 5 years of developing moderate albuminuria, one-third had progressed to severe forms of diabetic kidney disease, and by the 15-year mark, this cumulative progression had surpassed 50%. When factoring in the competing risk of death, 35.2% of the at-risk population had initiated kidney replacement therapy within 15 years of being diagnosed with severe albuminuria in the 1970s. Notably, this proportion had not fallen over time, as it stood at 35.6% in the combined 1980–99 cohort (Gray's test for difference $p = 0.37$). In other words, the progression rate of albuminuria remains high.[5]

Factors associated with the progression to kidney failure versus pre-kidney failure mortality were more closely examined among 592 FinnDiane Study participants with severe albuminuria at baseline. In these observational analyses, predictors of kidney failure (accounting for the competing risk of death and the baseline kidney function) were elevated glycosylated haemoglobin (HbA_{1c}), elevated low-density lipoprotein (LDL) cholesterol, male sex, weight-adjusted insulin dose and shorter diabetes duration. In contrast, factors associated with pre-kidney failure mortality (accounting for the competing risk of kidney failure and the baseline kidney function) were higher age,

the presence of established macrovascular disease and higher total cholesterol concentration.[6]

2.2 | Regression of albuminuria

Fortunately, progression is not the only possible direction of diabetic kidney disease, as also regression of albuminuria occurs (Figure 2). The estimated albuminuria regression rates in type 1 diabetes have ranged from minor fractions[8] to 50% and beyond,[9] depending on the study design and the specific definition of regression used.[4] We evaluated regression as a categorical trait in the FinnDiane cohort, defined as a change to a less advanced degree of albuminuria and assessed among 438 individuals with a history of moderate albuminuria and 475 with a history of severe albuminuria.[7] Altogether 102 study participants had regressed from moderate albuminuria to normal albumin excretion rate (AER) and 111 from severe albuminuria to less advanced kidney disease stages, meaning that the regression rate stood at 23%, irrespective of the initial albuminuria category.

The study further revealed beneficial long-term outcomes associated with albuminuria regression: both the incidence rates of cardiovascular events and premature mortality were reduced to the same level as for those whose kidney disease stage did not progress in the first place. These encouraging associations from the FinnDiane cohort align with observations from type 2 diabetes, showing that remission from moderate albuminuria translates into a significantly lower risk of a composite cardiovascular and kidney end point.[10] However, there is a major discrepancy compared to a study from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort, in which remission of moderate albuminuria did not impact the incidence of cardiovascular events.[11] The background of albuminuria regression, its natural history, as well as its clinical consequences thus warrant further investigation. Nevertheless, the findings from the FinnDiane Study highlight the importance of aiming for an AER as close to the normal levels as possible to improve the prognosis of individuals with type 1 diabetes.

2.3 | Various kidney disease phenotypes

While albuminuria often takes centre stage in early type 1 diabetes-related kidney disease, it is important not to overlook the other disease phenotypes, such as chronic kidney disease (CKD) without albuminuria. Due to the heterogeneous aetiology of CKD in type 2 diabetes, influenced by factors such as hypertension, obesity and age besides chronic hyperglycaemia, non-albuminuric kidney disease manifestation is prevalent in this population.[12] The background of kidney disease tends to be more uniform in type 1 diabetes; therefore, disease presentation without albuminuria is a less frequent phenomenon. Yet, the prevalence estimates vary substantially between studies.[13–15]

The prevalence of non-albuminuric kidney disease was only 2.0% in the FinnDiane cohort at the baseline study visit, and among those with established CKD (either increased albuminuria, estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2, or both), it affected 6.3% (Figure 3). Factors associated with this phenotype included older age, female sex, a history of retinopathy and cardiovascular disease. Non-albuminuric CKD increased the risk of cardiovascular events and all-cause mortality to the same extent as the albuminuria-only phenotype, but the highest outcome risk was noted among those with both albuminuria and eGFR <60 mL/min/1.73 m^2. The risk of kidney failure was no different in the non-albuminuric kidney disease group as compared to those free of kidney disease.[13]

3 | METABOLIC RISK FACTORS

The interplay between metabolic risk factors, kidney disease and the cardiovascular system, also called the cardiovascular-kidney-metabolic health, is recognized as an important factor driving poor prognosis in the general population and in people with type 2 diabetes.[16] In the following section, we will summarize the findings from the FinnDiane Study on the metabolic risk factors for diabetic kidney disease in type 1 diabetes. We will focus on the traditional metabolic risk factors related to metabolic syndrome.[17]

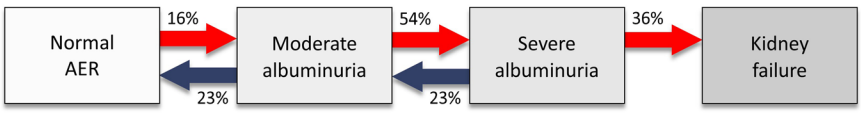

FIGURE 2 The updated natural history of diabetic kidney disease in type 1 diabetes, according to findings from a Finnish, population-based study as presented by researchers from the Finnish Diabetic Nephropathy (FinnDiane) Study. The 15-year cumulative progression rates are derived from the 1980–99 calendar year diagnosis cohort in Jansson Sigfrids et al.,[5] whereas the regression rates stem from Jansson et al.[7]

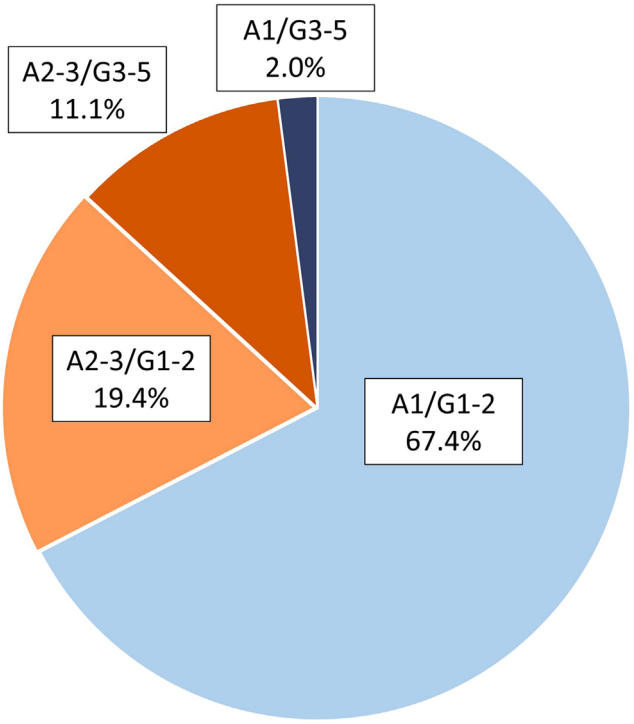

FIGURE 3 The various phenotypes of chronic kidney disease and their relative prevalences in type 1 diabetes, according to findings from the Finnish Diabetic Nephropathy (FinnDiane) Study. Figure adapted from Thorn et al.[13] A1 denotes normal to mildly increased albuminuria (albumin-creatinine ratio <3 mg/mmol, or albumin excretion rate <20 μg/min or <30 mg/24 h), A2–3 moderately to severely increased albuminuria (albumin-creatinine ratio ≥3 mg/mmol, or albumin excretion rate ≥20 μg/min or ≥30 mg/24 h), G1–2 normal to mildly decreased kidney function (eGFR ≥60 mL/min/1.73 m^2) and G3–5 impaired kidney function (eGFR <60 mL/min/1.73 m^2).

3.1 | Hyperglycaemia

The diabetic milieu is a prerequisite for the diabetic kidney disease to develop and poor glycaemic control is one of the main risk factors for diabetic kidney disease. The Diabetes Control and Complications Trial showed in the 1990s that improved glycaemic control, achieved by intensive insulin therapy, led to a 39% reduction in the incidence of moderate albuminuria and 54% in severe albuminuria.[18] The FinnDiane Study showed further, in an observational real-world setting, that high glycaemic variability, defined as the intrapersonal variability of HbA_{1c}, was equally detrimental for diabetic kidney disease development as poor glycaemic control. During 6 years of follow-up, the risk of diabetic kidney disease was the highest in those with both HbA_{1c} and the variability above the median, but was, interestingly, equally high for those with high variability, but HbA_{1c} below median, and those with low variability, but HbA_{1c} above median.[19]

TABLE 1 Assessment of insulin sensitivity in type 1 diabetes.

Assessment of insulin sensitivity in type 1 diabetes
The hyperinsulinaemic-euglycaemic clamp technique, the golden standard technique, is not feasible in clinical practice or large-scale studies.[22]
Common estimates of insulin sensitivity include fasting insulin and can, thus, not be used in people with type 1 diabetes that lack endogenous insulin (e.g. Homeostatic Model Assessment (HOMA-IR), Quantitavie Insulin Sensitivity Check Index (QUICKI) or simply fasting insulin).[22]
Type 1 diabetes-specific estimates of insulin sensitivity have been derived based on clinical variables. The most widely used is the estimated glucose disposal rate (eGDR) equation by Williams et al.,[23] later modified for the use of HbA_{1c} instead of HbA_1 for the FinnDiane Study[24]: • eGDR (mg kg^{-1} min^{-1}) = 24.4–12.97 × waist-to-hip ratio − 3.39 × hypertension − 0.60 × HbA_{1c} (%). • Hypertension stands for antihypertensive therapy and/or blood pressure ≥140/90 mmHg (yes = 1; no = 0).

3.2 | Insulin resistance

Insulin resistance, a central feature of type 2 diabetes, is present also in type 1 diabetes and already at the time of diabetes diagnosis. With the initiation of insulin therapy, the insulin sensitivity usually improves, but later in the disease process insulin sensitivity decreases.[20] This leads to the co-occurrence of both insulin deficiency and traits related typically more to type 2 diabetes, such as insulin resistance and related metabolic abnormalities, that is, double diabetes. This was shown also in the Diabetes Control and Complications Trial, where intensive insulin therapy resulted in substantial body weight gain in a subset of participants. This weight gain was accompanied by metabolic abnormalities, such as higher blood pressure, higher insulin requirements and dyslipidaemia, and in addition, associated with a positive family history of type 2 diabetes. Furthermore, this gain in body weight persisted also after the study closeout and translated into early signs of cardiovascular disease during follow-up.[21]

Diabetic kidney disease is an insulin-resistant state and insulin resistance also increases the risk of diabetic kidney disease. Insulin resistance (Table 1), measured by the clamp technique, has been shown to precede the onset of albuminuria in type 1 diabetes.[25] Insulin resistance assessed by the estimated glucose disposal rate (eGDR) equation has also been shown to increase the risk of overt diabetic kidney disease, defined as severely increased albuminuria or kidney replacement therapy.[26] More recently, data from the Swedish diabetes registry indicated that eGDR also predict albuminuria onset in people followed from early diabetes onset,[27] highlighting the role

of insulin resistance in the onset and progression of diabetic kidney disease. In the FinnDiane Study, we showed that eGDR decline (a sign of insulin resistance) follows the worsening of diabetic kidney disease, based on albuminuria severity and kidney function decline. Those with normal albumin excretion had generally preserved kidney function and normal insulin sensitivity, but those with moderately increased albuminuria were already more insulin resistant, while kidney function remained preserved, with no marked deterioration of insulin sensitivity with further albuminuria severity or decline in the estimated glomerular filtration rate. Although these observations demonstrate that insulin resistance precedes the decline in kidney function related to later stages of diabetic kidney disease,[24] the exact mechanisms connecting insulin resistance to albuminuria remain unclear.

3.3 | Metabolic syndrome

The clustering of cardiovascular risk factors related to insulin resistance is commonly denominated the metabolic syndrome. Traditional components of the metabolic syndrome include dysglycaemia, abdominal obesity, hypertension and dyslipidaemia, mainly as reduced high-density lipoprotein (HDL) cholesterol and elevated triglycerides. Different diagnostic criteria exist, but the most recent one, a joint statement by several organizations,[17] is the one we currently use in the FinnDiane Study (Table 2).

In addition to the classical components of the metabolic syndrome, other features have also been closely associated with the syndrome, interestingly including albuminuria as a component in the first definition suggested by the World Health Organization.[17]

Even before this first official definition of the metabolic syndrome, the individual components of the metabolic syndrome were noted to be associated with the vascular complications of type 1 diabetes,[30] highlighting the importance of insulin resistance-related traits in the pathogenesis of diabetic complications. The FinnDiane Study was the first to present data on the metabolic syndrome in type 1 diabetes, and we showed that the prevalence of the metabolic syndrome was 40% in adults with type 1 diabetes, with no difference between men and women, but with increasing prevalence with older age and worse glycaemic control,[24] sedentary lifestyle,[31] depression[32] and a history of parental type 2 diabetes.[33]

The metabolic syndrome is usually more strongly coupled to type 2 diabetes, but these findings from the FinnDiane Study[24,31–33] indicate that there are similarities in the metabolic syndrome observed in type 1 diabetes to that observed in people with type 2 diabetes. There are, however, some differences in the interplay between the metabolic abnormalities in type 1 and type 2 diabetes. In type 1 diabetes the hyperglycaemia is often more marked, and it also frequently precedes the onset of the other metabolic abnormalities, while in type 2 diabetes the metabolic abnormalities often precede the onset of diabetes. Another factor to consider when comparing the metabolic syndrome in the two types of diabetes is the impact of exogenous insulin administration in type 1 diabetes, leading to hypoinsulinaemia in the portal vein and subsequently affecting lipid metabolism, particularly by increasing HDL cholesterol levels.[34] For this reason, the low HDL

TABLE 2 Criteria for the metabolic syndrome adapted for people with type 1 diabetes.

For the metabolic syndrome, three of the following should be fulfilled	
Dysglycaemia	All people with type 1 diabetes fulfil this criterion due to diabetes diagnosis
Increased waist circumference[a]	Men ≥102 cm; Women ≥88 cm in Caucasians, Men ≥90 cm; Women ≥80 cm in Asians or Ethnic Central or South American
Elevated blood pressure	Systolic ≥130 and/or diastolic ≥85 mmHg, or antihypertensive therapy
Reduced HDL cholesterol	Men <1.0 mmol/L; Women <1.3 mmol/L
Elevated triglycerides	≥1.7 mmol/L or lipid-lowering therapy[b]

Note: The criteria are adapted from the joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity.[17]

[a]For waist circumference, there are different thresholds for different populations, and partly also for the same populations. For people with type 1 diabetes, we recommend higher thresholds since they are more sensitive to depict cardiovascular and kidney disease risk, at least in Caucasians.[28]

[b]We consider lipid-lowering therapy for the elevated triglycerides criterion since the effect of most lipid-lowering therapy is more profound for triglycerides than HDL cholesterol.[29]

cholesterol typically seen in the metabolic syndrome may signify a more 'extreme' form of metabolic disturbance in type 1 diabetes compared to type 2 diabetes.

Regarding the metabolic syndrome and diabetic kidney disease, the FinnDiane Study showed that the prevalence of the metabolic syndrome increases drastically with the kidney disease severity, being 28% in those without kidney disease, 44% and 62% in those with moderately and severely increased albuminuria, and 68% in those with kidney replacement therapy. The odds for diabetic kidney disease also increased by the number of fulfilled components of the metabolic syndrome and was 12-fold if all five components were present compared to only one or two components.[24] In the prospective setting, however, the metabolic syndrome was not a straight-forward predictor of diabetic kidney disease. The metabolic syndrome was not associated with increased risk of albuminuria onset or progression to severely increased albuminuria, but for progression to kidney replacement therapy, the metabolic syndrome and its components hypertension and elevated triglycerides increased the risk, while the abdominal obesity component was associated with decreased risk.[28] This highlights the paradoxical relationship between obesity and adverse events in severe illnesses, such as chronic kidney disease, where in some instances overweight or obesity is associated with better survival.

3.4 | Obesity

In line with the world-wide obesity epidemic, the proportion of overweight and obesity is steadily increasing also in people with type 1 diabetes. In the early years of the FinnDiane Study, only 8.5% were obese, but in recent years it has increased to 18.9%, and only 41.9% are normal weight.[35] In type 1 diabetes, body mass index (BMI) shows a U-shaped relationship with the development of diabetic kidney disease, with a higher risk in those with BMI below 22 and above 28 kg/m^2, and with indications of a causal link between obesity and the development of diabetic kidney disease in a Mendelian randomization analysis.[36] A similar U-shaped relationship is observed also for mortality risk, irrespective of the presence or absence of diabetic kidney disease.[35]

BMI is, though, not the best to capture cardiometabolic risk related to the metabolically most hazardous visceral fat, a key feature of central obesity and metabolic syndrome.[37] In the FinnDiane Study, we compared the different measures of obesity and central obesity with visceral fat mass measured with dual-energy x-ray absorptiometry (DXA). Of note was that visceral fat mass was higher in both men and women with albuminuria compared to those without. The best indicators for visceral fat mass were waist-height ratio and waist circumference, while BMI and waist-hip ratio performed less well in both sexes.[38] In the prospective setting, the FinnDiane Study showed that the waist-height ratio, with a common threshold of ≥0.5 in both men and women, was associated with diabetic kidney disease progression, and especially with new-onset albuminuria.[39] Abdominal obesity has also been linked to the onset of albuminuria in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, with 34% increased risk for every 10-cm increase in waist circumference, while no association was observed with the modest GFR decline during the same period.[40]

3.5 | Dyslipidaemia

Individuals with type 1 diabetes but without long-term diabetic complications, especially those with optimal glycaemic management, typically show no detrimental changes in their lipid profile. In fact, they may even exhibit better lipid control than the background population. This is a consequence of peripheral hyperinsulinaemia due to subcutaneous insulin administration, which increases the activity of the insulin-dependent lipoprotein lipase, thereby lowering triglyceride concentrations. The very low-density lipoprotein (VLDL) production is also down-regulated by the increased plasma insulin concentrations.[41]

On the other hand, in diabetic kidney disease, dyslipidaemia—and particularly hypertriglyceridaemia—is a frequent phenomenon, and the atherogenic lipid profile alterations of these individuals are believed to contribute to their excess cardiovascular disease burden. The link between dyslipidaemia and diabetic kidney disease has been extensively studied in the FinnDiane Study cohort.

Data from the FinnDiane Study have shown that in type 1 diabetes, not only impaired kidney function but also abnormally increased AER, even at low levels, is associated with lipid abnormalities. These observations originally stem from a cross-sectional analysis of 2927 study participants without kidney failure and lipid-lowering medication. Among the study participants with an eGFR below 60 $mL/min/1.73\,m^2$, the total cholesterol and triglyceride concentrations were higher and the HDL cholesterol concentrations lower than in those with normal (eGFR >90 $mL/min/1.73\,m^2$) or mildly impaired (eGFR 60–90 $mL/min/1.73\,m^2$) kidney function. The lipid profiles of those with mildly impaired kidney function were similar to those with normal kidney function.[42]

Associations between lipid profiles and the severity of albuminuria were evaluated using multiple linear

regression analysis. In the fully adjusted model including diabetes duration, HbA_{1c}, systolic blood pressure and eGFR, both triglycerides and HDL cholesterol were independently associated with AER. A similar link between AER and LDL cholesterol was also seen, however, this was not independent of eGFR. Across albuminuria categories, those with normal AER unsurprisingly exhibited the most favourable lipid profile. Total cholesterol and triglyceride abnormalities were seen already at the stage of moderate albuminuria. In the severe albuminuria group, all components of the conventional lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) showed detrimental alterations in comparison to the normal AER and moderate albuminuria groups.[42]

In observational, prospective analyses among 2304 FinnDiane study participants, high triglycerides but no other component of the lipid profile predicted incident albuminuria and progression from moderate to severe albuminuria in multivariable analyses, adjusted for traditional diabetic kidney disease risk factors. Yet, when baseline AER was added to the models, neither of these associations remained significant. High triglycerides were also predictive of progression from severe albuminuria to kidney failure, as were the high total cholesterol, high LDL cholesterol and low HDL cholesterol. However, when the eGFR was adjusted for, an independent association persisted for total cholesterol, but not for any other lipoprotein lipids.[43]

3.6 | Triglyceride- and cholesterol-imbalance of lipoproteins

Using proton nuclear magnetic resonance spectroscopy and a data-driven analysis approach, observations from the FinnDiane cohort have revealed a consistent pattern of lipoprotein lipid enrichment at all stages of diabetic kidney disease. The study investigated triglyceride and cholesterol contents of 14 lipoprotein subclasses, defined by particle size. In cross-sectional analyses, a 32%–69% higher triglyceride content across all VLDL subclasses was found, and analogously, the triglyceride content was 28% higher in intermediate-density lipoproteins (IDLs) and 22%–127% in HDLs among those with baseline severe albuminuria with the normal AER group as reference. Regarding the cholesterol content, significant enrichment was seen across the VLDL subclasses and small LDL, whereas the HDL lipoprotein classes were cholesterol-depleted compared to the reference population.[44]

In prospective analysis, incident albuminuria was associated with increased lipid content in large VLDL particles and progression from moderate to severe albuminuria with triglyceride enrichment of VLDL subclasses, IDL, large LDL particles, as well as HDL particles. Higher cholesterol concentrations in small LDL subclasses were also seen among the progressors. Those who further progressed to kidney failure exhibited a similar pattern of triglyceride enrichment among all VLDL, IDL and LDL lipoprotein classes, as well as higher cholesterol in the four largest VLDL subclasses. However, the cholesterol content was significantly lower in the medium-sized HDL subclass.[44]

The cholesterol content of triglyceride-rich lipoprotein particles, termed remnant cholesterol, has been of further interest in the FinnDiane Study population. The remnant cholesterol was calculated as the non-LDL, non-HDL cholesterol concentration, corresponding to the cholesterol content of the chylomicron remnants, VLDL and IDL particles. When examining observational, cross-sectional data, there was a clear trend of increasing remnant cholesterol concentrations as the albuminuria stage advanced. Those experiencing the progression of kidney disease during the prospective phase of the study had higher remnant cholesterol at baseline, and even after accounting for established risk factors like diabetes duration, HbA_{1c}, systolic blood pressure and smoking, remnant cholesterol remained independently linked to kidney disease progression. This association held true across all stages of kidney disease progression, with the exception of progression from severe albuminuria to kidney failure, which was independent of all other risk factors examined but not baseline eGFR.[45]

3.7 | Hypertension

Hypertension is a major contributing risk factor for the development of diabetic kidney disease in type 1 diabetes,[46] and the prevalence of hypertension increases in parallel with the worsening stage of kidney disease.[47] Elevated blood pressure is actually both a cause and a consequence of diabetic kidney disease; while the blood pressure rises along with the increase in albuminuria, high blood pressure also accelerates the loss of kidney function.[48] The FinnDiane Study reported for the first time that age-related changes in blood pressure (i.e. increase in systolic and decrease in diastolic blood pressure) occur 15–20 years earlier in individuals with type 1 diabetes than in non-diabetic controls.[49] Consequently, pulse pressure, a surrogate marker of arterial stiffness, increases earlier, suggesting accelerated arterial ageing among these individuals.[49] We have shown that pulse pressure is an independent risk factor for initial cardiovascular disease events across albuminuria categories;

yet, the pulse pressure did not predict the progression of diabetic kidney disease in adjusted analyses in the FinnDiane population, despite a univariable difference between progressors and non-progressors at baseline.[50] Although these age-related blood pressure changes are strongly related to the development of diabetic kidney disease, it should also be pointed out that even with normal AER, isolated systolic hypertension is three times more common in individuals with type 1 diabetes than in non-diabetic controls.[49]

3.8 | Diurnal variation in blood pressure

Several abnormal blood pressure patterns may indicate future kidney complications before any clinical symptoms appear.[51] These abnormalities may reflect disturbed diurnal blood pressure variability (e.g. non-dipping pattern or nocturnal hypertension) or disparities between office and out-of-office blood pressure measurements (e.g. masked hypertension).[51] Individuals are designated as non-dippers when the nocturnal fall is <10% of the daytime.[52] Non-dipping pattern of the systolic blood pressure is one of the earliest abnormalities of blood pressure profile detected in children and adolescents with type 1 diabetes; nearly half of them demonstrated a pathological systolic blood pressure dipping pattern.[53] Nocturnal hypertension often develops before the onset of albuminuria, but may also be an early predictor of albuminuria and sustained hypertension.[54] Both non-dippers and those with nocturnal hypertension have a higher likelihood to develop kidney complications than those with normal blood pressure pattern.[54]

Masked hypertension is characterized by a normal office, but elevated out-of-office blood pressure.[52] Compelling evidence suggests that masked hypertension is a high-risk phenotype, associated with an increased risk of target organ damage compared to those with normotension.[52] Results from the FinnDiane population and some other type 1 diabetes cohorts have shown that up to one-quarter of the individuals with type 1 diabetes have masked hypertension.[54,55] These studies have also shown an association between masked hypertension and arterial stiffness[55] and between masked hypertension and the development of moderate albuminuria and sustained hypertension.[54] As these disturbed blood pressure patterns are common and may play an important role in early diagnosis and management of hypertension, compared with office blood pressure or daytime home blood pressure monitoring alone, ambulatory blood pressure monitoring may provide an accurate tool to detect these abnormal blood pressure patterns among these high-risk individuals.[51]

3.9 | Blood pressure control

Although blood pressure control, especially with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, is extremely important to slow down or even halt diabetic kidney disease progression, many individuals with type 1 diabetes do not meet their recommended blood pressure targets. Most individuals with hypertension might require multiple antihypertensive drugs to reach their blood pressure targets. However, we observed in the FinnDiane Study that the majority of those with normal AER or moderate albuminuria who failed to achieve their blood pressure targets were treated with only one antihypertensive drug.[47] This might suggest either a suboptimal treatment regimen or poor adherence to the treatment. A subset of them might have treatment-resistant hypertension, a clinical condition characterized by failure to achieve the target blood pressure after taking a minimum of three antihypertensive drugs from different classes, one of which is a diuretic, or controlled blood pressure, but requires four or more antihypertensive drugs.[52] The FinnDiane Study showed that the presence and worsening of diabetic kidney disease rate increases the likelihood of treatment-resistant hypertension; while about 8% of those with normal AER or microalbuminuria met the criteria for treatment-resistant hypertension, the prevalence was about 40% in those on dialysis.[47] Although treatment-resistant hypertension was first established to improve the management of antihypertensive drug-treated individuals, since then many studies have shown the association between treatment-resistant hypertension and severe outcomes. The FinnDiane Study demonstrated that those with treatment-resistant hypertension had a two-fold risk of progression to a higher level of albuminuria compared to those with controlled blood pressure, after adjusting for clinical risk factors.[56]

4 | SUMMARY AND FUTURE DIRECTIONS

Improvements in prevention and treatment have led to a noticeable decrease in the incidence of diabetic kidney disease, but unfortunately, the progress seems to have reached a plateau. This stagnation is likely due to the lack of novel kidney-protecting medications since the introduction of renin–angiotensin–aldosterone inhibitors in the early 1980s. Additionally, the rising prevalence of obesity in recent decades may have countered any benefits of enhanced disease management, resulting in a stable rather than improving outlook. Furthermore, recent studies have revealed that those who develop diabetic kidney disease show no decline in the progression rate

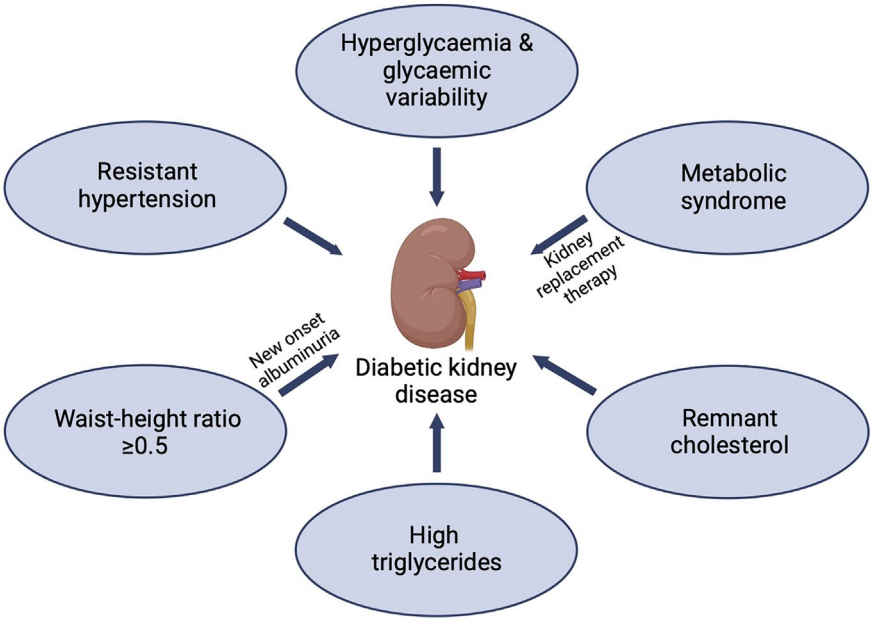

FIGURE 4 Metabolic risk factors associated with increased risk of diabetic kidney disease onset or progression in the Finnish Diabetic Nephropathy (FinnDiane) Study. Created with BioRender.com.

to initiation of kidney replacement therapy compared to the 1970s, highlighting the importance of efforts needed to prevent diabetic kidney disease in the first place and to find new treatment options for those who develop diabetic kidney disease.[5] With these alarming notes, there is still much to be done to improve outcomes for people with type 1 diabetes. Fortunately, some also regress regarding albuminuria, and this regression is associated with a more favourable prognosis.[7] The good news is that for people with type 1 diabetes without signs of kidney disease, the survival equals that of the general population.[57]

While the observational nature of the FinnDiane Study limits causal conclusions, its wide scope and real-world setting have provided important insights into how metabolic abnormalities, such as hyperglycaemia, insulin resistance, abdominal obesity, dyslipidaemia and hypertension parallel the worsening of diabetic kidney disease. How this interplay between the different metabolic risk factors is driving the kidney disease onset and progression is not entirely clear. Some risk factors, such as abdominal obesity seem to play a larger role in the onset of albuminuria, while the clustering of all risk factors, the metabolic syndrome, is more important at the later phases of the disease, increasing the risk of initiation of kidney replacement therapy. On the other hand, poor glycaemic control, increased glycaemic variability, hypertension, high triglycerides and remnant cholesterol are important both for diabetic kidney disease onset and progression (Figure 4).

For the prevention and treatment of diabetic kidney disease, the focus lies largely on the metabolic risk factors, both via lifestyle modification, risk factor control and pharmacotherapy.[58] For type 1 diabetes, many of the kidney-protective drugs, such as SGLT2 inhibitors, GLP-1 receptor agonist and non-steroidal mineralocorticoid receptor antagonists, are not approved.[58]

There is an urgent need for new treatment modalities in type 1 diabetes, including testing the benefit of available therapies and multifactorial interventions, as well as developing new treatment strategies, perhaps even such modalities that would be specifically developed for individuals with type 1 diabetes. There is also a suboptimal utilization of the available modalities, due to issues related to health care professionals, our health care system and patient compliance. Of the participants with diabetic kidney disease in the FinnDiane Study, 63% fail to reach the three key treatment targets HbA_{1c}, blood pressure and LDL cholesterol.[59]

The FinnDiane Study, as an observational comprehensively characterized cohort study, has a unique possibility to identify clinically relevant phenomena and provide data on incidence, risk factors and prognosis of different diabetes-related outcomes. With a mean follow-up of more than 20 years, the FinnDiane Study continues its mission to identify clinical, environmental and genetic risk factors for diabetic complications, with the goal of improving outcomes for people with type 1 diabetes.

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CONFLICT OF INTEREST STATEMENT

F.J.S. reports receiving lecture fees from AstraZeneca and Boehringer Ingelheim. P-H.G. reports receiving lecture fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, Merck, Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi and Sciarc. P-H.G. reports being an advisory board member for AbbVie, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Medscape, Merck, Sharp& Dohme, Mundipharma, Nestlé, Novartis, Novo Nordisk and Sanofi. No other potential conflicts of interest relevant to this article were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Fanny Jansson Sigfrids https://orcid.org/0000-0002-1192-348X
Raija Lithovius https://orcid.org/0000-0001-7313-4710
Per-Henrik Groop https://orcid.org/0000-0003-4055-6954
Lena M. Thorn https://orcid.org/0000-0003-3999-0390

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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