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Critical Review

Contrasting Effects of Type 2 and Type 1 Diabetes on Plasma RBP4 Levels: The Significance of Transthyretin

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Summary

Retinol-binding protein 4 (RBP4) is the principle carrier of retinol in the human plasma, which circulates as a complex with transthyretin (TTR), a homotetrameric thyroxine transport protein. Although this complex formation is thought to prevent glomerular filtration of RBP4, it also stabilizes the quaternary structure of TTR. Recent studies indicate elevated plasma levels of RBP4 in type 2 diabetes (T2D). In contrast, reduced RBP4 levels were observed in type 1 diabetes (T1D). Herein, we critically examine the probable mechanisms involved in the regulation of RBP4 and TTR levels during T2D and T1D. The available evidences point to the involvement of pancreatic factors in regulating the expression of both RBP4 and TTR. It appears that during T1D, TTR levels are reduced and it exists predominantly as a monomer that may interfere its interaction with RBP4 resulting in its loss through glomerular filtration. However, plasma TTR levels remain high under T2D conditions and thus reducing glomerular filtration of RBP4. Therefore, the plasma TTR levels appear to be an important determinant of plasma RBP4 levels in these two diabetic conditions.

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Keywords vitamin A; RBP4; TTR; diabetes; glomerular filtration.

INTRODUCTION

Diabetes and obesity are public health concerns all over the world associated with several comorbidities. Type 1 diabetes (T1D) is characterized by absolute insulin deficiency resulting from autoimmune destruction of pancreatic β-cells, whereas type-2 diabetes (T2D) is a heterogeneous metabolic disorder resulting from decreased sensitivity of target tissues to insulin. Obesity, characterized by excessive body fat, has been found to be an important risk factor for the development of insulin resistance (*1, 2*). Adipose tissue, the central player in obesity, was initially thought to be an inert organ meant only for energy storage in the form of triglyceride. However, it is now recognized as an active endocrine and paracrine organ playing important roles in the development of metabolic syndrome during obesity (*1, 2*).

Mature adipocytes are known to secrete an ever-increasing number of proteins, collectively known as adipokines, which participate in diverse physiological and pathophysiological processes such as inflammation, coagulation, fibrinolysis, insulin resistance, atherosclerosis, and some forms of cancer (*1, 2*). Proinflammatory molecules secreted by the adipocytes such as tumor necrosis factor-α, monocyte chemotactic protein-1, interleukin-6, leptin, and resistin have been implicated in obesity-induced insulin resistance, whereas adiponectin, an anti-inflammatory molecule, improves insulin sensitivity. Obesity is widely considered as a state of chronic low-grade inflammation and is found to be strongly associated with elevated levels of proinflammatory adipokines (*1, 2*). Conversely, a reduction in the body weight is associated with a decrease in the plasma levels of most of these proinflammatory adipokines (*1, 2*). However, whether the modulation of these specific adipokine levels in the plasma is a cause or a consequence of obesity and/or insulin resistance remains to be established.

Plasma retinol-binding protein (also termed as RBP or RBP4) is the sole carrier of vitamin A (*all trans*-retinol) in circulation. In the blood, RBP4 circulates as a complex with thyroxine-binding protein, the transthyretin (TTR), which increases the apparent molecular mass of RBP4 complex, and thus prevents its glomerular filtration (*3, 4*). Recently, RBP4 expression in adipocytes has been reported to be related to its plasma levels. Elevated plasma RBP4 levels appear to be positively associated with insulin resistance, T2D, and dyslipidemia (Table 1). Although the role of RBP4 in vitamin A transport is well appreciated over the years,

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Table 1
Contrasting effects of type 1 and type 2 diabetes on plasma, RBP4, TTR, and retinol levels

Physiological status	Experimental model	Retinol-binding protein	Transthyretin	Retinol	Reference
Type 2 diabetes	Mice and humans	High	–	–	Yang et al. (*5*)
Type 2 diabetes	Humans	High	–	–	Graham et al. (*14*)
Type 2 diabetes	Humans	High	–	–	Cho et al. (*15*)
Type 2 diabetes	Humans	High	–	High	Aeberli et al. (*18*)
Type 2 diabetes	Humans	High	–	High	Erikstrup et al. (*26*)
Type 2 diabetes	Humans	High	High	–	Kloting et al. (*16*)
Type 2 diabetes	ob/ob mice	High	High	–	Mody et al. (*28*)
Type 2 diabetes	Humans	–	–	High	Krempf et al. (*24*)
Type 1 diabetes	Humans	–	–	Low	Krempf et al. (*24*)
Type 1 diabetes	Humans	Low	–	Low	Basu et al. (*40, 41*)
Type 1 diabetes	Humans	–	Low	–	Reffai et al. (*29*); Itoh et al. (*32*)
Type 1 diabetes	Humans	Low	–	Low	Krill et al. (*39*)
Type 1 diabetes	STZ-treated rat models	Low	Low	Low	Basu et al. (*47*); Tuitoek et al. (*49*)
Type 1 diabetes	BB rats	Low	Low	Low	Lu et al. (*48*); Chen et al. (*51*)

its implication in the development of insulin resistance has fueled further interest in this area. Interestingly, in contrast to T2D, the plasma RBP4 and retinol levels were found to be lower in T1D in humans and in streptozotocin (STZ)-induced diabetic animal models (Table 1). The opposing influence of T2D and T1D on plasma RBP4 levels infer an underlying role of pancreatic function in regulating the vitamin A homeostasis or at least plasma vitamin A levels. Herein, we critically examine the role of RBP4 in vitamin A transport and the modulation of plasma RBP4, TTR, and retinol levels in T2D and T1D disease states in order to provide key insights and possible mechanisms that may explain the diabetes-induced dichotomy on plasma RBP4 levels.

ROLE OF RBP4 AND TTR IN VITAMIN A METABOLISM

Retinol is an essential component in the physiology of vision and plethora of other biological functions (*3, 4*). As retinol is insoluble in water, it is transported by RBP4, a 20-kDa protein, from its storage site liver to the various target tissues. It has been reported that apo-RBP4 preferentially accumulates in the liver during vitamin A deficiency, implying that retinol–RBP4 complex formation within the hepatocyte is a prerequisite for RBP4 secretion into the blood (*3*). In the blood, RBP4 circulates as a complex with a 55-kDa homotetrameric thyroid hormone transport protein, the TTR. It is believed that such protein–protein interaction increases the apparent molecular mass of RBP4–TTR complex and thus prevents its loss through glomerular filtration. This structure–function relationship was further strengthened by the observation that TTR knockout mice exhibit lower plasma RBP4 levels and higher urinary excretion of RBP4 (*3, 4*). Furthermore, *in vitro* studies demonstrated that retinol–RBP4 complex, but not apo-RBP, binds to TTR (*3*). In tune with these results, fenretinide, a drug that competes with retinol for binding to RBP4, inhibits its interaction with TTR and increases its renal clearance (*3, 5*). Interestingly, knockouts of either RBP4 or TTR are viable, suggesting the existence of efficient compensatory mechanisms for the transport of retinol and thyroid hormones (*3, 4*).

Although the liver is the major storage depot of retinol, about 15–20% of the total body retinol is found to be resident in the adipose tissue (*3, 4*). The expression of RBP4 mRNA and protein was demonstrated in several extrahepatic tissues including adipocytes (*3, 5*). Moreover, in mice lacking lecithin:-retinol acyltransferase, large amount of retinyl esters remain in the adipose tissue that are mobilized during dietary retinoid insufficiency (*4*), implying an important role of adipose tissue in retinol storage and mobilization.

It has long been postulated that cellular retinol uptake from RBP4 is a facilitated, receptor-mediated process (*3, 4*); however, the mechanism of RBP4-dependent vitamin A uptake in tissues and cells remained elusive for a long time. Recently, a multitransmembrane domain protein named "stimulated by retinoic acid 6" (STRA6) was identified as the long-sought RBP4 receptor, which binds and catalyzes the retinol transfer from RBP4 (*6*). Mutations of *STRA6* have been reported to cause the fatal Matthew-Wood syndrome, characterized by pleiotropic, multisystem malformations that include cardiac deformities and ocular defects (*6*). Such dramatic consequences of *STRA6* defi-

ciency were unanticipated because RBP4-deficient patients and knockout mice displayed only a mild clinical phenotype that included night blindness and moderate retinal dystrophy (*3*). The discrepancy between the STRA6- and RBP4-deficient phenotypes suggests that STRA6 is required in additional hitherto unknown vital processes (*6*).

RBP4 AND ITS LINK TO DIABETES

In general, with the increase in the blood glucose concentrations following a meal, the insulin levels increase to enhance the clearance of glucose by inducing the translocation of glut-4 (an insulin-responsive glucose transporter) to plasma membrane in muscle and adipose tissue (*5, 7–9*). Therefore, reduced glut-4 level in adipose or muscle is considered as a hallmark of insulin resistance (*5, 7–9*). Interestingly, mice with adipose-selective ablation of *glut-4* had normal growth and adipose mass despite markedly impaired insulin-stimulated glucose uptake in adipocytes (*8*). Interestingly, these mice developed insulin resistance in muscle and liver despite preserved *glut-4* expression (*8*). This indicates that insulin resistance in the adipose tissue due to reduced mobilization of glut-4 to the membrane induces secretion of some factors that could mediate global insulin resistance.

To identify the supposedly adipocyte-derived insulin-antagonizing factors, Yang et al. (*5*) generated mice that either lacked adipose *glut-4* or have elevated levels of *glut-4* in adipose tissue, and by using cDNA microarray analysis, they found that several genes, including RBP4, showed opposing expression patterns in these mice. The RBP4 expression in adipose tissue was found to be inversely related to *glut-4* expression in adipose tissue. Further studies demonstrated that in diet-induced and genetic rodent models of obesity (ob/ob and db/db), the circulating RBP4 levels are increased 2.8-fold and 13-fold, respectively (*5*). RBP4 mRNA levels in the adipose tissue were also found to be reduced on treatment with an antidiabetic drug, rosiglitazone, which reverses insulin resistance in mice with selective ablation of adipose-*glut-4* (*5*). Mice injected with RBP4 were found to express higher levels of phosphoenolpyruvate corboxykinase (PEPCK) in liver, suggesting that RBP4 induces gluconeogenesis and thereby contributes to increased blood glucose levels (*5*). Based on these studies, it was suggested that reduced glut-4 and/or reduced glucose uptake in adipose tissue induces synthesis and secretion of RBP4 from adipose tissue, which in turn causes insulin resistance in muscle and liver. In agreement with these observations, treatment with fenretinide, a drug that induces urinary clearance of RBP4, was found to ameliorate insulin resistance. Similarly, RBP4 knockout mice displayed better insulin sensitivity when compared with the mice that had higher expression of RBP4 in muscle (*5*). These interesting studies in animal models provided a strong mechanistic basis for the involvement of RBP4 in the pathophysiology of obesity and insulin resistance.

Corroborating with the above observations, supplementation of retinoic acid to ob/ob mice reduced plasma RBP4 levels by increasing its renal clearance and thus improving insulin sensitivity (*10*). Furthermore, genetic polymorphisms in RBP4 are also found to be associated with higher risk of development of T2D (*11*). Suppression of RBP4 expression in liver and adipose tissue using anti-RBP4 RNA oligonucleotides led to reduced plasma RBP4 levels and to improved insulin sensitivity in mice with high-fat diet-induced metabolic syndrome (*12*). Recently, it has been demonstrated that binding of RBP4 with STRA6 triggers the downstream JAK2-STAT5 signaling cascades, leading to inhibition of insulin signaling and PPAR-γ (*13*). These studies suggest a role for RBP4 and possibly its receptor STRA6 in the development of insulin resistance and provide a strong mechanistic basis for antidiabetic therapies targeting the plasma RBP4 levels. However, direct effects of RBP4 on insulin-stimulated glucose uptake either in adipocytes or in muscle are yet to be demonstrated. Therefore, it is possible that increased gluconeogenesis in the liver due to RBP4 (*5*) might represent a potential mechanism by which RBP4 contributes to hyperglycemia. Nevertheless, the exact molecular mechanism that leads to increased plasma concentrations of RBP4 during insulin resistance and the source of the increased plasma RBP4 (liver or adipose) during obesity and/or insulin resistance remains to be understood.

PLASMA RBP4, TTR, AND RETINOL LEVELS IN TYPE 2 DIABETES

Interestingly, these findings in mice are also reconcilable with those in human subjects. The study by Graham et al. (*14*) demonstrated that elevated plasma RBP4 levels are associated with increased body mass index, waist-to-hip ratio, plasma triglyceride levels, and systolic blood pressure and decreased levels of high-density lipoprotein cholesterol in humans. Increased physical activity leads to reduction in RBP4 levels and is inversely correlated with *glut-4* mRNA levels in adipocytes (*14*). Cho et al. (*15*) demonstrated that plasma RBP4 concentrations were higher in the impaired glucose tolerance and T2D groups than in the normal glucose tolerance group. Furthermore, plasma RBP4 levels were found to be associated with sex, waist circumference, fasting plasma glucose, and insulin resistance. These observations coupled with direct effects of RBP4 demonstrated in animal and cell culture models (*5, 13*) imply a strong role of RBP4 in obesity-mediated insulin resistance. Recently, extensive trials in insulin-resistant adults and children from multiple ethnic backgrounds revealed a strong association between plasma RBP4 concentrations with insulin resistance, obesity, and metabolic syndrome components (*16–20*). In addition, interventions that ameliorate insulin resistance in humans also reduced plasma RBP4 levels (*11, 14, 21–23*). However, a few studies failed to establish a correlation between insulin resistance and plasma RBP4 levels, probably due to several confounding variables such as genetic background, age, sex, and general nutritional status of the study subjects apart from methodological problems in assessing RBP4 levels (*11*).

Similar to RBP4, plasma retinol levels were also found to be higher in T2D subjects when compared with the normal healthy

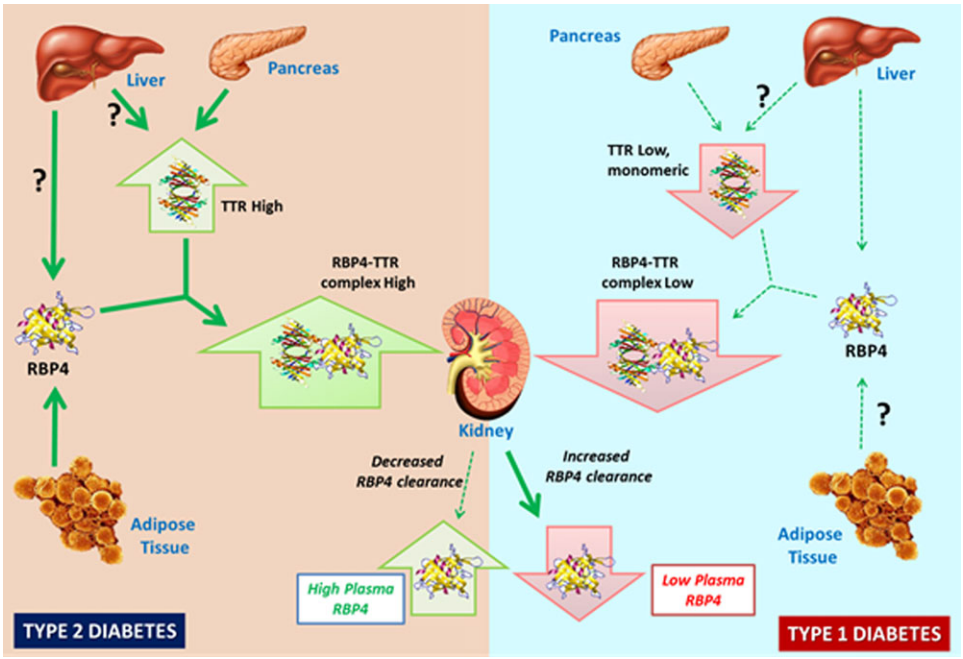

Figure 1. Schematic representation of dichotomy of plasma RBP4 levels in type 1 and type 2 diabetes. During T2D, the retinol-binding protein (RBP4) levels in plasma are elevated as a result of their increased expression in adipose tissue, and TTR levels are also simultaneously increased due to increased pancreatic and hepatic synthesis. The formation of RBP4–TTR complex prevents glomerular filtration of RBP4 and thus elevates its plasma concentrations. In contrast, during T1D, the hepatic output of RBP4 and TTR is impaired along with decreased expression of pancreatic TTR, which results in the decreased formation of RBP4–TTR complex. The free RBP4 is subsequently lost through increased glomerular filtration, leading to an overall decrease in the plasma RBP4 concentrations. Thick and continuous arrows represent higher expression, and thin and dashed arrows indicate decreased expression. The "?" marks indicate insufficient information on expression/secretion of RBP4 and TTR from tissues. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

controls (*24*). In addition to increased plasma retinol and RBP4 levels, increased expression of β-carotene monooxygenase-1 (BCMO1) was observed in diabetic rat liver and intestine. BCMO1 is known to accelerate conversion of β-carotene to retinol during insulin resistance states, which to some extent explains the observed high levels of plasma retinol in these rats (*25*). However, in some studies, plasma RBP4 levels were reported to be in excess of retinol, and elevated RBP4/retinol ratio is found to be a better predictor of insulin resistance rather than RBP4 levels alone (*11, 26*). As binding of retinol is an absolute necessity for RBP4 secretion from tissues (*3*), it is possible that increased tissue uptake of RBP4–retinol complex might lead to transient elevation of plasma apo-RBP4 levels. However, till date, no information is available on the expression of STRA6 (RBP4 receptor) under these conditions. In a recent study, a G>A single-nucleotide polymorphism in *STRA6* was found to be significantly associated with elevated risk of development of T2D in a South Indian cohort (*27*). This mutation is predicted to alter the trafficking and cell surface expression of this protein, thus suggesting a critical role of STRA6 in the development of insulin resistance. Mody et al. (*28*) also demonstrated decreased renal clearance and elevated plasma RBP4 levels in ob/ob mice as a result of increased plasma TTR concentrations. Furthermore, higher plasma TTR concentrations were also observed in humans with obesity and/or insulin resistance (*16*). Increased levels of TTR mRNA and protein have been demonstrated in both pancreatic β- and α-cells during T2D (*29–32*). Therefore, it is possible that elevated plasma TTR levels (possibly derived from pancreas) prevent the renal clearance of RBP4, leading to insulin resistance. Furthermore, stress and glucocorticoids associated with increased insulin resistance are also known to induce TTR expression in liver and choroids plexus (*33, 34*). Interestingly, renal failure associated with increase in plasma RBP4 levels was also reported to be linked with insulin resistance (*35*).

These results together suggest that elevated levels of plasma RBP4 in obesity and T2D could be due to either increased RBP4 expression in the adipose tissue or increased plasma TTR levels or both (Fig. 1). TTR probably serves as a regulatory checkpoint for insulin function by modulating plasma RBP4 levels.

PLASMA RBP4, TTR, AND RETINOL LEVELS IN TYPE 1 DIABETES

Mosenthal and Loughlin (*36*) first reported that the plasma retinol levels are depleted in T1D, and these observations are

subsequently confirmed by others (*24, 37, 38*). In a family-based study, Krill et al. (*39*) reported significantly lower mean plasma retinol and RBP4 levels in T1D subjects when compared with nondiabetic subjects despite similar dietary intakes of vitamin A. Furthermore, the low retinol phenotype also appears to be heritable among T1D subjects, suggesting an inherent metabolic link between T1D and vitamin A transport. Basu et al. (*40, 41*) also reported declined plasma vitamin A levels in T1D adults. Interestingly, plasma levels of vitamin A in diabetic patients as well as in the control subjects showed a significant linear regression with plasma concentrations of RBP4, suggesting incomplete mobilization from liver stores or increased renal clearance of RBP4 (*40, 41*). However, in these subjects, the plasma vitamin E concentrations remained normal, implying specific alterations in the vitamin A transport during T1D (*40*). Wako et al. (*42*) demonstrated that reduced plasma levels of retinol are accompanied by increased concentrations of retinyl esters in T1D patients suggesting a decreased hepatic output of vitamin A. Interestingly, higher plasma carotenoids and retinyl ester levels were observed in T1D (*43*), pointing to impaired conversion of carotenoids to vitamin A. Similarly, in STZ-treated T1D rat models, the BCMO1 activity in liver was reported to be reduced, whereas in intestine, the activity remained unchanged (*44*). These observations in clinical settings unequivocally establish an inverse relationship of T1D with plasma retinol/RBP4 levels, which is in contrast to T2D.

Although plasma retinol and RBP4 levels in plasma of T1D subjects are reduced when compared with their normal counterparts, it did not manifest subclinical vitamin A deficiency (*40, 41*). Alternatively, urinary excretion of both RBP4 and retinol was found to be elevated in T1D subjects even under conditions of normoalbuminurea (*45, 46*), suggesting that increased renal filtration might also account for reduced plasma RBP4/retinol levels (Fig. 1).

Similar to those observed in humans, decreased plasma retinol, RBP4, and TTR levels were observed in genetic and STZ-induced T1D rat models, with consequent increase in hepatic concentrations when compared with the nondiabetic animals (*41, 47–50*). The factors that may affect blood retinol status include its dietary intake, absorption, and the proteins related to the intrahepatic retinol metabolism or transport. Neither the intake nor the intestinal absorption of vitamin A was found to be affected in T1D (*41, 50*). In fact, the intake of food and hence vitamin A is markedly increased in STZ-induced diabetic rats (*41, 50*). Interestingly, the hepatic concentrations of retinol remained high in these diabetic animals, which were further elevated when supplemented with vitamin A, indicating a blockade of vitamin A mobilization that is solely dependent on RBP4 (*47, 48, 51*). This is further supported by the observation that retinyl ester hydrolase activity in liver was found to be decreased in T1D rat models, but not in intestine, in agreement with increased hepatic accumulation without changes in the intestinal absorption of retinol (*51*). It is also possible that the decrease in plasma retinol and/or RBP4 could be a result of increased renal filtration due to low plasma TTR concentrations during T1D (*40, 41*). It has been reported that plasma TTR concentrations were depressed in newly diagnosed T1D human subjects as well as in T1D rat models (*29, 32, 41*). Interestingly, the concentrations of monomeric form of TTR are higher in T1D when compared with normal subjects, but not the tetrameric TTR (*32*). Therefore, it appears that reduced TTR concentration might elevate renal clearance of RBP4/retinol during T1D, leading to reduced plasma levels of RBP4 (Fig. 1). In contrast, the decrease in the functional tetrameric TTR could also be due to reduced plasma RBP4 levels, as RBP4 is known to stabilize the tetrameric structure of TTR (*4*). These results clearly suggest an impaired metabolic availability of vitamin A during T1D, which could be a ramification of either impaired mobilization of liver retinol stores or increased renal clearance of RBP4 (Fig. 1).

THE EFFECT OF INSULIN AND GLUCAGON ON RBP4 AND TTR EXPRESSION AND THEIR PLASMA LEVELS

It is clear from the above discussion that two different diabetic states that are essentially characterized by lack of insulin action (T2D) or insulin deficiency (T1D) influence the plasma RBP4 and TTR levels in opposite directions (Table 1). Therefore, it would be logical to believe that either insulin or some other pancreatic factor dictate the circulating RBP4 levels and consequently vitamin A levels either by regulating the RBP4 synthesis/secretion or by modulating its renal clearance. In addition, acute-phase response and the nutritional status of individuals may also contribute to the reduced RBP4 levels observed in T1D (*3*). It has been shown that administration of insulin can lower the hepatic storage of vitamin A in T1D animal models (*49*). In addition, zinc is also known to induce the secretion of RBP4 from liver, and zinc deficiency leads to secondary vitamin A deficiency due to accumulation of RBP4 in the liver (*4*). In general, T1D is also reported to be associated with low plasma zinc levels. However, insulin, but not zinc supplementation, improved plasma concentrations of RBP4 in STZ-induced diabetic rats (*41, 49*). Furthermore, pancreas transplantation in T1D patients also reported to improve the serum RBP4 levels along with glycemic status (*52*), implying that insulin, glycemic status, and possibly other pancreatic factors may modulate plasma RBP4 levels. In contrast to the above observations, *in vitro* studies with isolated rat islets and *in vivo* studies involving depletion and repletion of vitamin A in rats have demonstrated that retinoids are required for insulin and glucagon secretion (*53, 54*). Therefore, whether insulin regulates vitamin A transport or vitamin A regulates insulin expression/secretion remains a matter of debate. Nonetheless, insulin and glucagon levels in the RBP4 knockout mice were normal when compared with the wild-type counterparts (*5*), suggesting that the retinoids may not be involved in the insulin secretion *per se*. Moreover, STRA6, the RBP4 receptor, is expressed at the sites of insulin action

like muscle and liver, but not reported either in pancreas or in β-cells.

In general, insulin and glucagon are functionally antagonistic to regulate the blood glucose levels. Because insulin treatment normalizes the plasma vitamin A levels during T1D (*49*), glucagon is expected to reduce the same. However, glucagon also appears to increase the RBP4 synthesis in cultured hepatocytes and in liver through intracellular cAMP and activation of high-mobility group A1 gene (*55*). Interestingly, in contrast to insulin, glucagon levels are reported to be high in both T1D and T2D states, and there is lack of suppression of glucagon release in hyperglycemic conditions, which would further contribute to the postprandial hyperglycemia (*56, 57*). However, this irregular α-cell behavior does not occur when insulin levels are normalized, suggesting that abnormalities in glucagon release are relevant for hyperglycemia in the context of diabetes or impairment of insulin secretion or action (*56*). Therefore, it is likely that insulin/glucagon ratio might influence the plasma RBP4 levels in normoglycemic conditions either by controlling its expression in the liver/adipose tissue or by regulating its glomerular filtration through plasma TTR.

THE POSSIBLE PHYSIOLOGICAL BASIS AND RELEVANCE OF RBP4 MODULATION DURING TYPE 2 AND TYPE 1 DIABETES

From the above review, it is evident that plasma RBP4, TTR, and serum retinol levels are conversely regulated under T2D and T1D states (Table 1). It is possible that increased expression of RBP4 during obesity and T2D in adipocytes might account for its increased plasma levels. Lack of glucose in adipocytes (due to insulin resistance) might switch RBP4 synthesis (*5*), which in turn acts on liver to improve the blood glucose levels. Although RBP4 was demonstrated to interfere with insulin signaling in adipocytes (*13*), its effect on insulin-induced glucose uptake was not demonstrated. Therefore, RBP4 might be relevant in maintaining the fasting glucose concentrations by modulating glucose output from the liver. Considering this notion, the plasma RBP4 levels should also be high in T1D due to inherent hyperglycemia and lack of insulin. However, studies in human and animal models consistently demonstrated reduced plasma RBP4 and retinol levels in T1D. Interestingly, pancreas transplantation or insulin treatment not only normalized the plasma RBP4 levels but also the blood glucose levels in T1D (*49, 52*), suggesting a role for pancreatic factors, particularly insulin or glycemic status in modulating plasma RBP4 levels. However, insulin treatment of T1D subjects did not influence the synthesis rates of RBP4 (*58*). Therefore, mechanisms such as regulation of RBP4 renal clearance that are dependent on insulin or glycemic status might explain this dichotomy. Interestingly, expression of TTR was reported in both pancreatic α- and β-cells and was shown to be upregulated during T2D, whereas it was downregulated during T1D (Table 1), providing a strong case that argue for pancreatic TTR role in the modulation of plasma RBP4 levels. Moreover, TTR is found to be stored in the secretory vesicles in pancreatic islets, thus it is likely that part of the plasma TTR is derived from the pancreas (*29–32*). Furthermore, TTR is known to be inducible by insulin-like growth factor-1, and an insulin-responsive element has also been identified in the TTR promoter region (*59*). Therefore, while it is possible that TTR expression is upregulated under high-insulin conditions (T2D), the converse is true in T1D. Hence, differential regulation of plasma TTR during T2D and T1D might explain the dichotomy of RBP4 levels in T2D and T1D states (Fig. 1).

CONCLUSIONS

The available experimental and clinical evidences clearly point to an association of plasma RBP4 levels to that of insulin resistance and metabolic syndrome components. In addition to its classical retinol carrier function, RBP4 seems to be involved in increasing the hepatic glucose output by activating PEPCK and by inhibiting the insulin signaling pathways. Increased carotene conversion activity due to higher expression of BCMO1 and higher RBP4 expression in adipose tissue appear to be involved in the enhanced plasma RBP4 levels in T2D. In contrast to T2D, the concentrations of serum RBP4 and retinol in T1D subjects and animal models were reported to be declined because of reduced BCMO1 expression, mobilization and increased renal clearance of RBP4. These divergent effects of T2D and T1D on plasma retinol and RBP4 levels strongly suggest a metabolic link between pancreatic function and vitamin A homeostasis. Interestingly, the changes in retinol and RBP4 levels in T2D and T1D are concurrent with the changes in plasma TTR levels. Although the effect of T2D and T1D on liver TTR expression remains unknown, the expression patterns of TTR in pancreas in T2D and T1D appear to reflect the changes in plasma TTR concentrations. As plasma TTR prevents the loss of RBP4 through glomerular filtration, the opposing effects of T2D and T1D on plasma RBP4 levels could be best explained by changes in the plasma TTR concentrations. Furthermore, the monomeric TTR, the predominant form in the plasma, during T1D might also perturb its interaction with RBP4 and thus contributes to its increased loss through glomerular filtration.

Although this review highlights the crosstalk between pancreatic function and vitamin A metabolism, in particular the perplexing status in T1D and T2D, further investigations are warranted to understand the nexus between vitamin A metabolism and diabetes. For example, understanding the influence of insulin and other pancreatic factors on carotene conversion, vitamin A absorption and tissue distribution, intrahepatocyte metabolism of retinol, RBP4 synthesis, and modulation of RBP4 half-life in the plasma will throw light on the regulation of vitamin A metabolism and its link to energy metabolism. As TTR regulates the plasma RBP4 levels, whether reducing the plasma TTR levels could form the basis of antidiabetic therapies needs to be explored.

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