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Novel insights and an updated review of metabolic syndrome in immune-mediated organ transplant rejection

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Metabolic syndrome (MetS) is a group of symptoms that are characterized by abnormal changes in metabolic substances such as glucose, lipids, proteins, and bile acids. MetS is a common complication after organ transplantation and can further affect the survival and physiological function of the graft by reprogramming the patient's immune environment. Additionally, MetS can influence the occurrence of post-transplant complications, such as infections. In recent years, research into the epidemiology and mechanisms of MetS has grown significantly. In this review, we summarize the mechanisms of MetS after transplantation and the mechanisms of hyperglycemia, insulin resistance, hyperlipidemia, abnormal bile acids, and abnormal amino acids on the body's immune cells as related to the effect of metabolic disorders on immune rejection after liver, kidney, heart, skin and other organ transplantation. Finally, we provide an overview of current treatment strategies and offer insights into potential future therapies for managing MetS in transplant recipients.

KEYWORDS

metabolic syndrome, organ transplantation, transplant rejection, immune system, metabolites and immune cell

1 Introduction

Metabolic syndrome (MetS) was first proposed in 1988 and is characterized by dyslipidemia, hypertension, and insulin resistance (IR) in a hypertriglyceride-low HDL-cholesterol state; with the development of this research, the scope of metabolic abnormalities has gradually increased (1). Organ transplantation is still the best method for the treatment of end-stage organ failure. In recent years, due to improvements in surgical techniques and postoperative management, the survival rate of transplant patients has significantly increased (2). However, metabolic abnormalities, such as blood glucose, blood lipids, and amino acids, that often occur after transplantation strongly affect the survival of grafts and the quality of

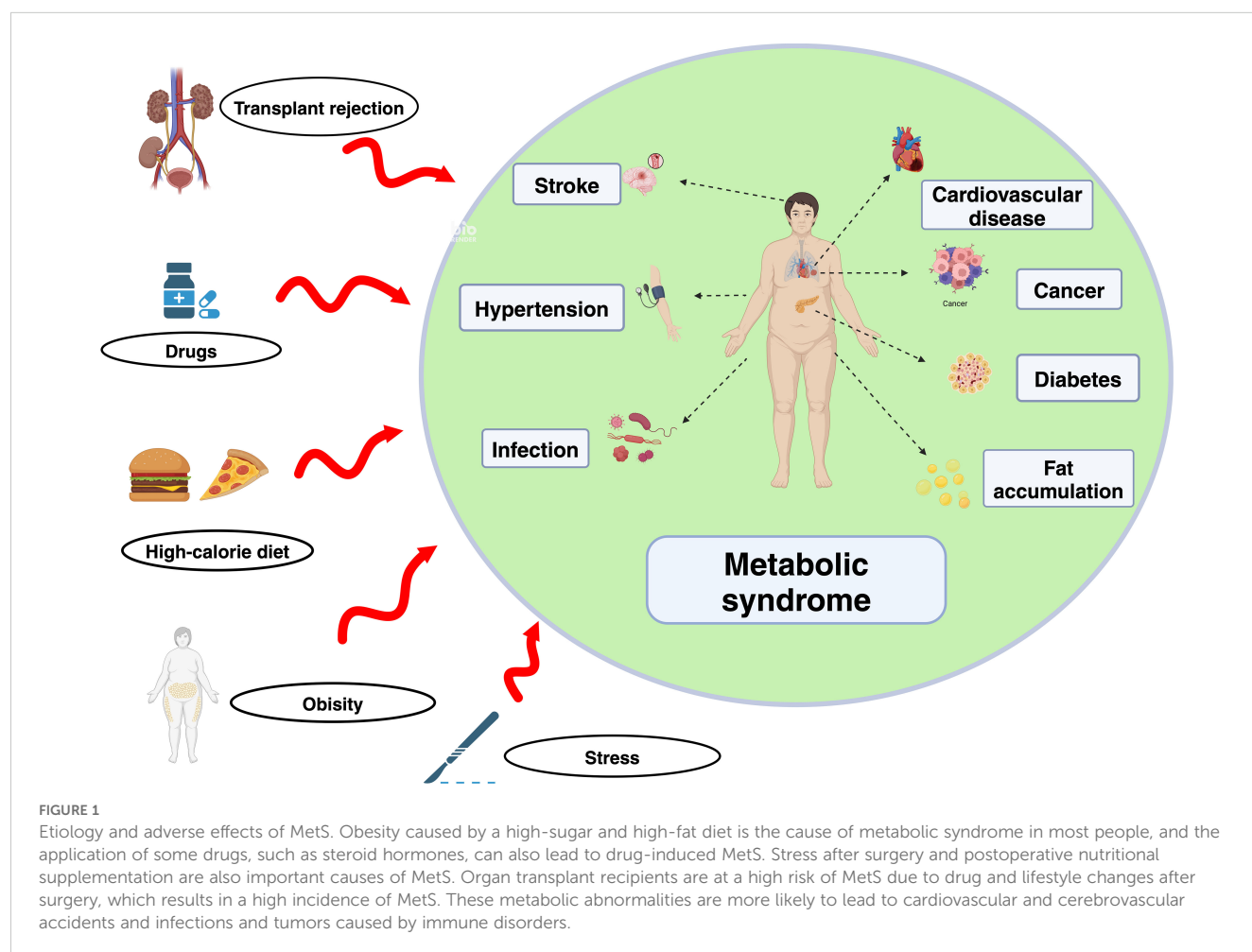
life of patients. Among the latest diagnostic indicators of metabolic syndrome, waist circumference is usually used as an indicator of abdominal obesity to establish a rough estimation. Comprehensive evaluations of fasting serum triglyceride, high-density lipoprotein, and cholesterol levels; blood pressure; fasting blood glucose; and other indicators are needed to further determine risks (1, 3). Current studies have shown that stress caused by transplantation surgery, drug and lifestyle changes after transplantation, and a series of metabolic abnormalities that occur before and after transplantation have regulatory effects on the immune system, which alters the normal immune environment in different ways and affects the immune tolerance and tolerance of the graft. The result is reduced graft survival time, cardiovascular disease risk, infection, cancer, hypertension and other complications (Figure 1) (3).

In this review, we summarize the current impacts of MetS on transplant immune rejection. Starting with the pathophysiological mechanism of MetS, we first discuss the impact of the abnormal metabolism of lipids, sugars, bile acids, and amino acids in MetS on immune cells and immune signaling pathways in the immune system. Then, we discuss the relationship between organ transplant rejection and MetS. Finally, current management strategies and prospects for transplantation are discussed.

2 Pathophysiological mechanisms of MetS

2.1 Mechanisms of insulin resistance

Insulin is a peptide hormone secreted by pancreatic beta cells in response to elevated blood glucose. Its main role is to promote the ability of effector cells to store glucose as glycogen in the liver and skeletal muscle and to convert glucose into fatty acids and lipids, ultimately resulting in decreased blood glucose (4). As a result of surgical stress and the side effects of immunosuppressive drugs, the reduced insulin sensitivity and insulin secretion of effector cells often leads to insulin transplantation resistance and posttransplant diabetes (5). When insulin resistance occurs in skeletal muscle, the inhibition of insulin-mediated lipolysis is reduced, the oxidative breakdown of fatty acids is increased, and the increase in free fatty acids (FFAs) further inhibits the function of PI3 kinase and GLUT-4 in the insulin transport pathway and exacerbates insulin resistance (6–8). Increased FFAs also cause cholesterol and triglyceride (TG) levels to increase, which further causes TG levels to shift from vLDL to HDL and reduces HDL



concentrations (9). Abnormal blood lipid changes can lead to the activation of macrophages and the deposition of cholesterol in blood vessels, which leads to pathological changes in atherosclerosis in MetS patients (10). Moreover, an increase in FFAs leads to a decrease in brachial artery dilatation function and hypertension in MetS patients (11); additionally, insulin resistance in MetS patients increases blood viscosity (12).

2.2 Secretory mechanisms in adipose tissue

Adipose tissue is a tissue with endocrine properties and its dysfunction is one of the main causes and pathogenic mechanisms of MetS. A variety of cytokines and hormones, such as TNF- α , IL-6, and IL-8, as well as plasminogen activator inhibitor-1, angiotensin-II, adiponectin, and leptin, are secreted (13).

Generally, adipose tissue plays a key role in MetS. The role of leptin is related to the inhibition of food intake and increasing energy expenditure (14) and it has also been linked to the activation of immune function and cardiovascular and cerebrovascular diseases (15, 16). In chronic hyperleptinemia and leptin resistance, continuous stimulation of the sympathetic nerve by leptin leads to vasospasm and hypertension, and leptin can further change sympathetic nerve excitability by regulating renal Na excretion. Additionally, in chronic hyperleptinemia, it can indirectly influence the occurrence of heart disease by enhancing platelet aggregation and fibrinolytic injury and promote angiogenesis (16) and it has become a key molecule linking obesity, MetS and cardiovascular injury. Adiponectin is another important molecule that is secreted by adipose tissue and plays important antiapoptotic, insulin sensitivity, anti-inflammatory and antifibrotic roles (17). Some studies have shown that its deletion may lead to MetS in mice (18). Another adipokine secreted by adipocytes, chemerin, has been implicated in inflammation, adipogenesis, angiogenesis, and energy metabolism in individuals with MetS (19). Small cohort studies have shown that the level of chemerin is greater in individuals with *de novo* MetS (20–22), which suggests that chemerin may be involved in the development of MetS.

2.3 Other relevant molecular mechanisms

As a widely studied cytokine, IL-6 can be secreted by a variety of cells, such as adipocytes and lymphocytes, in MetS (23, 24). Studies have shown that IL-6 has a steroid-like effect, which can affect lipid metabolism by affecting macrophage recruitment, improving insulin resistance (25), and enhancing adrenal function (26). Moreover, it also acts on the circulatory system and can affect mitochondrial function, which can lead to atherosclerosis (27). TNF- α can be secreted by adipose tissue (23), and macrophages that accumulate in adipose tissue are an important source of TNF- α release (28). The increased release of TNF- α (29), which can affect insulin action through the NF- κ B, IKK- β and JNK systems (30, 31), serine phosphorylation, and loss of downstream receptor molecules

(32), has been reported in obese and insulin-resistant patients. The proinflammatory effects of TNF- α on the arterial wall suggest that it also plays a key role in atherosclerosis (31). Moreover, with increasing intracellular cAMP, intracellular fatty acid breakdown and the concentration of FFAs increase (33).

As a secreted protein, Fetuin-A is involved in a variety of metabolic processes and its association with MetS has attracted increasing attention (34). Increased secretion of Fetuin-A has been observed in adipose tissue and the viscera of obese patients (35, 36) and has been shown to induce insulin resistance by interfering with GLUT-4 and activating Akt (37).

2.4 Mechanisms of gut microbiota metabolism

In recent years, the mechanisms underlying the relationship between gut microbiota and the development of MetS have garnered significant attention. Gut microbiota can induce and exacerbate MetS through multiple pathways, including influencing nutrient absorption, promoting chronic inflammation, and disrupting bile acid homeostasis. The balance between pathogenic and beneficial microbiota is fundamental to maintaining metabolic stability; however, this equilibrium is often disrupted in MetS (38–40). One of the consequences of dysbiosis in gut microbiota is chronic inflammation. Under the combined effects of external factors and inflammation, the integrity of the intestinal barrier is compromised, allowing endotoxins produced by pathogenic bacteria to enter the systemic circulation more easily, thereby inducing low-grade systemic inflammation (41, 42). When external factors lead to gut microbiota dysbiosis, the expression of LPS increases, driving Toll-like receptor (TLR) signaling, degrading the mucosal layer, and triggering endotoxemia. This process promotes the production of trimethylamine (TMA), a pro-atherogenic metabolite, ultimately contributing to metabolic dysregulation (43, 44).

Bile acids, as endocrine signaling molecules, exert critical regulatory roles in glucose and lipid metabolism through nuclear farnesoid X receptor (FXR) and membrane-bound G protein-coupled receptor 5 (TGR5). Beyond facilitating the absorption of lipid-soluble nutrients, they orchestrate multiple metabolic processes including glucose homeostasis, lipid regulation, and energy balance. Dysregulation of bile acid metabolism significantly contributes to the pathogenesis and progression of MetS (45). Bile acid biosynthesis is mediated via two primary enzymatic pathways: cholesterol 7 α -hydroxylase (CYP7A1) and sterol 27-hydroxylase (CYP27A1), whose expression is modulated by microbial activity (46, 47). Emerging evidence indicates that gut microbial communities enriched in bile salt hydrolase (BSH)-producing species hydrolyze conjugated bile acids into diverse secondary forms, thereby establishing an expanded bile acid pool with enhanced functional complexity (48, 49).

Dietary interventions modulate gut microbial composition, subsequently reshaping bile acid metabolism. Specific microbiota subpopulations eliminate endogenous FXR antagonists such as

tauro- β -muricholic acid (T β MCA), thereby potentiating FXR signaling. Concurrently, these microbial consortia generate secondary bile acids (e.g., deoxycholic acid and lithocholic acid) that act as potent ligands for TGR5 (50). Mechanistically, TGR5 activation enhances energy expenditure via thermogenesis in brown adipose tissue and skeletal muscle, while concurrently stimulating glucagon-like peptide-1 (GLP-1) secretion from intestinal L cells. Notably, L cells co-express FXR, which transcriptionally regulates GLP-1 synthesis, establishing a synergistic crosstalk between FXR and TGR5 signaling in metabolic regulation (47, 51).

2.5 Etiology and mechanisms of MetS after transplantation

The main cause of dyslipidemia after transplantation is the use of immunosuppressive drugs; for example, the use of corticosteroids can lead to hyperlipidemia through increased appetite, insulin resistance, and increased synthesis of triglycerides and cholesterol. Calcineurin inhibitors cause hyperlipidemia by reducing bile acid excretion, inhibiting insulin secretion and increasing FFAs. The side effects of mTOR inhibitors on the development of hyperlipidemia are greater than those of calcineurin inhibitors. The application of mTOR inhibitors mainly leads to an increase in triglycerides and leads to an increase in FFAs, which is associated with the inhibition of LPL, decreased catabolism of apolipoprotein B-100-containing lipoproteins, and excessive production of VLDL-C (52–54).

The incidence of post-transplantation diabetes mellitus (PTDM) is associated with obesity, insulin resistance and race. Specifically, certain races may be more sensitive to immunosuppressive agents. Older age, higher blood lipid levels, and an inflammatory state are also important factors for the development of PTDM in African American patients (55). The immunosuppressive drugs that are calcineurin inhibitors, cyclosporine and tacrolimus, can also cause PTDM through glucose transporter 4 (GLUT4), changes to glucokinase function that induces β -cell apoptosis, and blockage of the nuclear factor of activated T cells (NFATc) and other mechanisms (2). The contribution of tacrolimus to the development of insulin resistance is relatively high because it binds to the high level of FK506-binding protein in pancreatic β cells and inhibits insulin secretion (53). Steroids decrease the sensitivity of the liver to insulin, which leads to increased gluconeogenesis so that even when the pancreas releases insulin, the liver continues to release glucose, leading to increased appetite, fluid retention, and weight gain (56). Genetic studies have shown that peroxisome proliferator-activated receptor α (PPAR α) is an important regulator of glucose and lipid metabolism and donor PPAR α gene polymorphisms affect susceptibility to metabolic disorders after liver transplantation (57). A persistent graft–host immune response and immunosuppression-mediated infection, which induce islet β -cell apoptosis, are also involved in the pathogenesis of PTDM (58, 59).

Obesity not only causes the induction of PTDM before transplantation but is also a common complication after transplantation. Obesity can affect carbohydrate metabolism or aggravate diabetes by increasing insulin resistance after

transplantation, and obesity is more likely to cause postoperative atherosclerosis (60). Increased visceral fat in obese individuals can lead to metabolic abnormalities through the secretion of inflammatory adipokines and thereby increase the risk of cardiovascular accidents (61). Weight gain before transplantation increases the rate of transplant failure, prolongs the duration of transplant surgery, and leads to proteinuria after transplantation, which eventually leads to obesity-related chronic kidney disease (Figure 2) (62).

3 Effects of MetS on the immune system

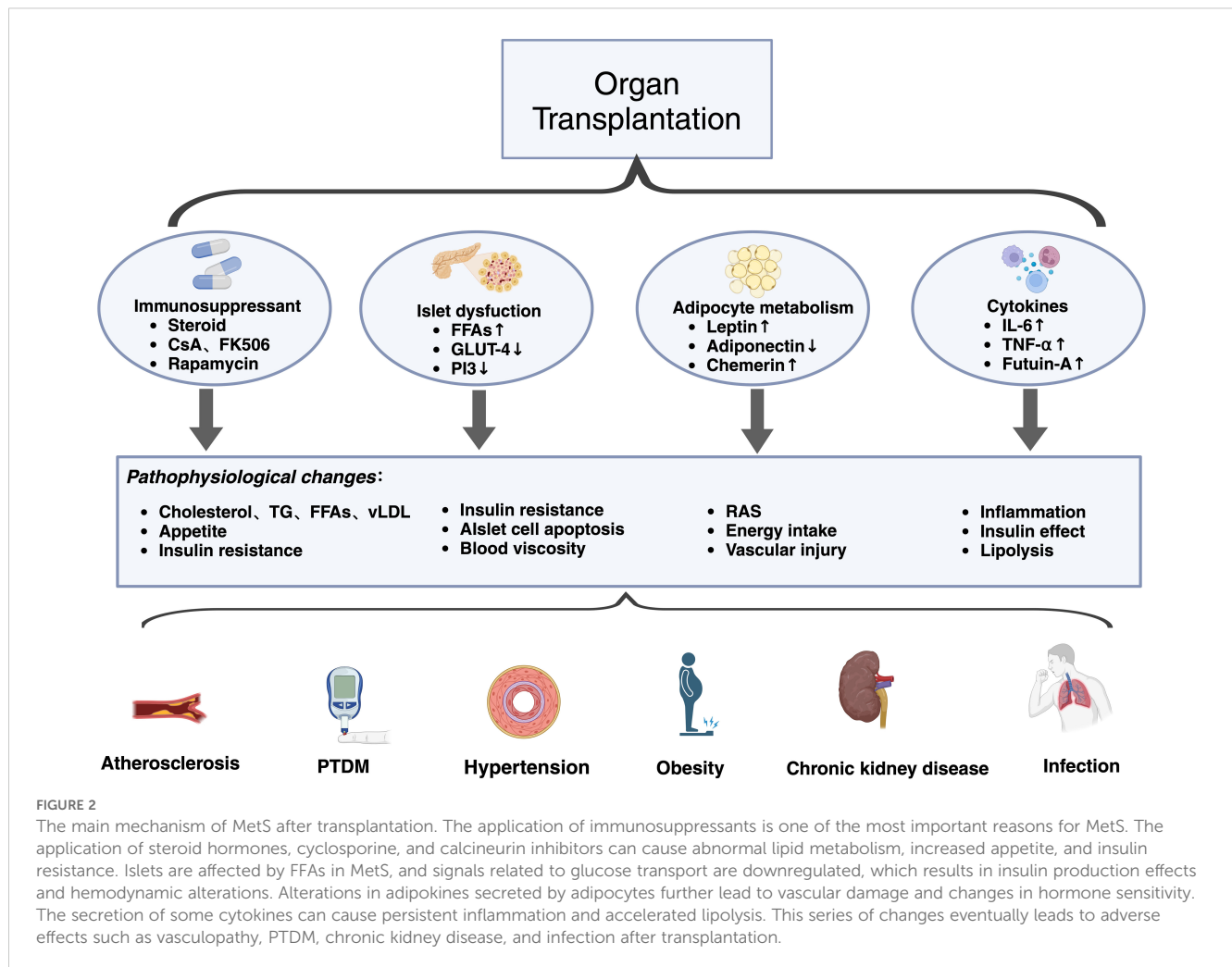
The proliferation, differentiation, and functional activity of immune cells are fundamentally regulated by the dynamic equilibrium of the immune microenvironment (63, 64). MetS perturbs this equilibrium through dysregulation of metabolites and signaling molecules via the aforementioned pathophysiological pathways. Notably, MetS significantly alerts the critical metabolic components within the immune microenvironment, including insulin signaling, carbohydrate homeostasis, lipid profiles, bile acid dynamics, and amino acid availability (1). These metabolites orchestrate immune cell differentiation and function, inducing bidirectional regulation in immune cell phenotypes toward pro-inflammatory and anti-inflammatory states (Table 1).

Previous research has predominantly focused on the incidence of post-transplant metabolic syndrome (PTMS) in relation to patient survival, complications, and graft functional outcomes (65, 66). However, the impact of PTMS on immune cell dynamics and the immune microenvironment remains underexplored. Emerging evidence indicates that PTMS induces sustained immune system activation, characterized by elevated and persistent chronic inflammatory burden, which correlates with adverse clinical prognoses (67). Concurrently, PTMS-driven metabolic dysregulation promotes hyperactivation and tissue infiltration of immune cells, a phenomenon mechanistically linked to vasculopathy and hepatic complications in transplant recipients (68–71).

3.1 Effects of hyperglycemia and hyperinsulinemia on immunity

3.1.1 Effects of hyperglycemia on T cells

Diabetes is a common complication after transplantation (72). Although hyperinsulinemia enhances the ability of memory CD8 T cells to regulate GLUT-1 and promote glucose uptake, the direct effect of hyperglycemia on memory T-cell function is predominant in diabetes. Furthermore, it can reduce the secretion of cytokines without reducing the proliferation of memory T cells or the function of memory T cells (73). Hyperinsulinemia activates effector CD8+ T cells and insulin signals through PI3K, and in this process, insulin stimulation enhances the costimulatory effect of CD28, which further enhances effector T-cell action (74, 75). In



patients with insulin resistance, the downstream pathway of insulin receptor (INSR) signaling may be depleted and insulin-stimulated AKT signaling may be reduced, which may be related to a decrease in T-cell immunity (76). In hyperglycemia, increased activation of the MAPK pathway in T cells leads to enhanced cytokine production, proliferative phenotypes and chromatin decondensation (77).

3.1.2 Effects of hyperglycemia on B cells

Under the influence of diabetes, the B-cell repertoire is altered, which leads to immune confusion (78). B cells present a more proinflammatory phenotype, IL-6 and TNF-α are increased, and IL-10 secretion is decreased. However, the antibody reactivity of B cells is decreased, which is not consistent with the proinflammatory phenotype of B cells (79). Another study revealed elevated levels of IgA, IgM, and total antibodies produced by B cells in the vitreous of the eye (80). Other studies have reported that insulin resistance can damage the metabolic phenotype of B cells, increase the volume of mitochondria in cells, change the structure of the cristae, and reduce the mitochondrial respiratory function of B cells. The result is that the production of plasma cells is inhibited, and B-cell immunity is reduced (81).

3.1.3 Effects of hyperglycemia on macrophages

Macrophages are divided into proinflammatory M1 macrophages and anti-inflammatory M2 macrophages. Under conditions of high blood glucose, macrophages are more prone to M1 polarization. The decreased release of protective inflammatory factors, such as Arg-1 and CD206, and increased expression of proinflammatory markers, such as IL-6, iNOS, and TNF-α, as well as metabolites like the α-dicarbonyl and AGER pathways (82–84), have been reported. Hyperglycemia promotes the expression of proinflammatory M1-associated IL-6, which increases the immune capacity of macrophages. This effect is associated with metabolic changes driven by epigenetic reprogramming, which may be caused by epigenetic changes in multiple genes caused by lactic acid (82, 85). It is also possible that the expression of histone methyltransferases SMYD3 and SET7/9 upregulates the epigenetic regulation of S100A12 to upregulate the expression of S100A9 and induce an activated histone code at the corresponding gene promoters in M1 macrophages. Enhanced macrophage responses to Toll-like receptor (TLR) ligands include palmar folate (PA), lipopolysaccharide (LPS), and proinflammatory stimuli (86). In a study comparing diabetic and nondiabetic macrophages,

TABLE 1 Mechanism of metabolic influence on immunity.

	Effector cells	Subsets of cells	Mechanism	Related molecules and pathways	References
Abnormal Insulin metabolism	T cells	Memory T cells	Hyperinsulinism stimulates GLUT-1 expression, enhances glucose transport, and accelerates glucose uptake	GLUT-1	(73)
		CD8 T cells	Hyperinsulinemia increased the cytokine secretion of T cells under the costimulation of CD28	CD28	(75)
		Effector CD4 T cells CD8 T cells	Insulin resistance leads to the loss of INSR signaling, the downstream signaling of T cells is inhibited, and the function is down-regulated	INSR	(76)
Abnormal glucose metabolism		Memory T cells	Under hyperinsulinism, the expression of CD127 molecules, the differentiation of memory CD8 T cells and the secretion of cytokines were decreased	CD127	(73)
			Activation of the MAPK pathway enhances proliferation and effector capacity, and leads to chromatin decondensation	MAPK	(77)
	B cells	Plasma cells	Mitochondrial structure is altered, respiratory function is reduced, and plasma cell immunity is suppressed	mTOS	(81)
	Macrophages		Hyperglycemia promotes the transformation of macrophages into M1 and induces persistent inflammatory expression after epigenetic changes	MLL H3K4 methyltransferase enzymes	(82, 85)
			Epigenetic changes in macrophages induced by hyperglycemia lead to proinflammatory responses	SMYD3 SET7/9 S100A12 S100A9	(86)
			The high glucose environment induces immune memory in mitochondria	LC3bBeclin-1 RhoA/ROCK	(87, 88)
			Hyperglycemia promotes M1 transformation, inhibits M2 phenotype, and promotes inflammation development.	STAT CD163 Acsl1 Notch FoxO1 CCL18 IRF8 NF-κB/Caspase-1	(90–92, 95, 96, 98)
			Hyperglycemia induces pyroptosis of macrophages	ser-ulk1-757 mTORC1	(97)
			Under hyperglycemia, macrophage mechanosensitivity and cytokine secretion are increased	TLR4/LPS	(99)

(Continued)

TABLE 1 Continued

	Effector cells	Subsets of cells	Mechanism	Related molecules and pathways	References
Abnormal lipid metabolism	T cells	Treg cells	Hyperlipemia promotes the proliferation of Treg cells	FOXP3	(106, 110, 111)
			High cholesterol inhibits the proliferation and differentiation of iTreg and nTreg	HIF-1 α Foxp3 mtROS	(113)
			High cholesterol inhibits Treg cells differentiation	ABCG1 p-STAT5/Foxp3	(115–117)
		Th17	High cholesterol inhibits the proliferation of Th17 cells by activating LXR	LXR ABCG1 srebp-1	(119, 120)
		CD4 T cells	High cholesterol activates LXR and enhances the T plasma membrane lipid raft profile	LXR UGCG	(118)
		Tfh cells	High cholesterol activates LXR β , which in turn affects CD4T cells and ultimately leads to the restriction of Tfh differentiation	LXR GSK3 β TCF-1	(121)
			Triglyceride stimulated Th1, Th17 and CD4 T proliferation and differentiation <i>in vitro</i>	CD36	(122, 123)
	B cells	Plasma cells	High cholesterol inhibits plasma cells differentiation through SREBP2 expression	SREBP2	(124)
			High cholesterol induces multiple pathways leading to B-cell expansion	LXR α LXR β CD11c+ APC BM SDF-1:CXCR4 CD53/TSPAN25/MOX44	(127–129)
	NK cells		High cholesterol activates NK cells killing through multiple pathways	NCR1 NKG2D STAT ERK	(130)
			High cholesterol inhibits NK cell-related pathways	c-Myc/P300 H3K27ac	(131)
			High TG reduces CD36 expression and NK cells activity	PI3K-Akt-mTOR/FOXO1 CD36	(132)
	macrophages		Hyperlipidemia negatively regulates inflammation by inhibiting the increase of protein kinase C delta	pAkt PKC δ	(136, 137)
			Hyperlipidemia can promote the expression of CD80 on macrophages and affect NKT induced inflammation	CDd CD80	(138)
					(136, 139, 140)

(Continued)

TABLE 1 Continued

	Effector cells	Subsets of cells	Mechanism	Related molecules and pathways	References
			Hyperlipidemia promotes inflammation by promoting CD36 expression and PCSK9 expression	PCSK9 CD36	
			Hyperlipidemia induces macrophages to suppress inflammation through external vesicles	ApoE miR-146a-5 miR-142a-3p	(141)
			Hyperlipidemic endoplasmic reticulum stress promotes M1 polarization	IRE1 α	(143)
			Hyperlipidemia related metabolic pathway changes	Bmp2 Cx3cl1 Tlr6	(142)
	neutrophil		Hyperlipidemia accelerates neutrophilic inflammation	BM SDF-1:CXCR4 CCR1 CCR2 CCR5 CXCR2	(128, 145, 146)
			Hyperlipidemia accelerates neutrophil mobilization	NOD1	(147)
	dendritic cells		Hyperlipidemia induces DC to express ligands to regulate the functions of NK, Treg and CD4 T cells	PD-L1 TGF- β 1 NKG2D RXRA TSLP ox-LDL cDC2	(132, 148, 150, 152)
			Activation of DC by ox-LDL	TLR4/MyD88-NF- κ B ox-LDL TLR IL-12p4	(149, 151)
	Abnormal amino acid metabolism	T cells	Glutathione can regulate the expression of PD1 in T cells	PD-1/PD-L1	(155, 156)
			A variety of amino acids can cause T cell immune disorders	mTOR	(153, 154, 158)
		Th17 cells	Glutaminase activates Th17 to induce inflammatory response	GLS1	(160, 161)
		Memory T cells	Citrulline cycling promotes CD8 memory T cells development	Kbhb Cps1	(159)
		CD4 T cells	Homoarginine affects the protein skeleton to regulate the function of CD4T cells	Myh9	(162)
		Dendritic cells	Tryptophan regulates Treg cells by regulating DC	IDO	(157)

(Continued)

TABLE 1 Continued

	Effector cells	Subsets of cells	Mechanism	Related molecules and pathways	References
	macrophages		Amino acids affect mitochondria and then affect the differentiation of macrophages into M2 type		(163)
Abnormal metabolism of bile acids	T cells	Th17 cells	3-oxoLCA inhibited Th17 differentiation	ROR γ t	(165, 175)
		Treg cells	3-oxoLCA enhances Treg differentiation	mitoROS FoxP3	(165)
			The intestinal BA pool affects Treg cells responses	BA-VDR ROR γ	(167)
			isoalloLCA enhances iTreg cells differentiation	NR4A1 mTROS Foxp3	(173)
		CD3 + CD8 + T cells	TCA inhibited CD3 + CD8 + T cells activity		(174)
		CD8 cytotoxic T cells	DCA reduced CD8 cytotoxic T cells function	PMCA NFAT2	(166)
			UDCA affects the transcription and antigen presentation of T cells	FXR TGR5	(168)
			CDCA increased the expression of FXR, and DCA inhibited the expression of FXR, which affected the activation of T cells	FXR store-operated Ca ²⁺ NFAT	(59, 169, 170)
			CBA and Mdr1 induce immune equilibrium	Teff Mdr1	(171)
		Th1	LCA inhibits Th1	VDR ERK-1/2	(172)
	macrophages		TCA induced the transformation of macrophages into M2 type	SIRT5	(176)
			CDCA inhibited the transformation of macrophages into M2	ROS/p38 MAPK/DGAT1	(177)
			UDCA induced the transformation of macrophages into M2	NF- κ B FXR	(178)
			DCA and CDCA promoted macrophage M1 transformation	NLRP3 FXR	(180)
			Multiple bile acids activate TGR5 to promote M2 transformation	TGR5	(175)
	NK cells		TCA inhibited NK cells activation	NKG2D	(174)
			TLC inhibited NK cells migration		(179)

researchers reported that the autophagy proteins, LC3b and Beclin-1, which maintain mitochondrial homeostasis in normal macrophages, were downregulated in diabetic macrophages. This phenomenon suggests that macrophages may adapt to long-term hyperglycemia and that its downregulation may reduce mitochondrial homeostasis, which is closely related to the increase in reactive oxygen species (ROS) in hyperglycemic conditions (87, 88). A study on the promotion of inflammation in macrophages by hyperglycemia revealed that macrophages take up CD163, which inhibits the uptake of Hb-Hp1-1 and Hb-Hp2-2 by macrophages and thus produces a vascular protective effect (89). Simultaneously, Arg1 and Mrc1 gene induction and subsequent STAT3 and STAT6 signaling activation are reduced (90). Another study revealed that the transcription of Acs11 mRNA was induced in macrophages and hyperglycemia alleviated the repression of CHREBP, which further promotes Acs11 transcription and leads to a proinflammatory response (91). Moreover, hyperglycemia can lead to the upregulation of Notch, which further promotes M1 transformation and exacerbates inflammatory injury (92). High blood glucose can induce the activation of Raw264.7 macrophages, participates in the activation of the MAPK pathway, and increases the secretion of TNF- α and macrophage adhesion (93). The activation of LPS involved in phagocytosis under high-glucose conditions led to a slight increase in the expression of the CD36 gene under normoxia and normoglycemia, and the expression of inflammatory factor-related genes was upregulated (94). Furthermore, it promoted the inflammatory phenotype of macrophages by attenuating FOXO1-activated IL-10 expression (95). M2 cells are limited in their ability to differentiate because of the inhibition of CCL18 production (96). These changes in metabolic pathways lead to the transition of macrophages to the M1 type. Researchers have shown that high glucose stimulates mTORC1 activation and ser-ulk1-757 activation, which induces pyroptosis, but these changes have no effect on macrophage activation (97). High-glucose conditions induce macrophage senescence and SASP factor secretion through NLRC4 phosphorylation, which further stimulates the NF- κ B/Caspase-1 cascade through an IRF8-dependent pathway (98). Similarly, LPS enhances Acs11 promoter activity through NF- κ B, CHREBP and p65/RELA to promote inflammation (91). Studies have shown that the mechanical sensitivity of macrophages to high glucose is also increased. With increasing substrate stiffness, the expression of the related proinflammatory genes TLR4/LPS also increases, and the secretion of TNF- α increases (99).

3.2 Effects of hyperlipidemia on immunity

3.2.1 Effects of hyperlipidemia on T cells

Cholesterol plays a major role in the composition and fluidity of the cell membrane and affects the differentiation and function of immune cells (100). Cholesterol metabolism is associated with T-cell proliferation (101), and sterol response element binding protein (SREBP) on the ER membrane of T cells is a sensor for T cells to sense lipids. Under low-fat conditions, it binds to SREBP cleavage

activator protein (SCAP) and enters the nucleus, where it increases the expression of synthetic-related enzymes, such as hydroxymethylglutaryl (HMG)-CoA reductase (HMGCoR) and low-density lipoprotein receptor (LDLR), and also enhances endogenous cholesterol uptake. Under high-fat conditions, the insulin-inducible gene protein (INSIG) present in the ER membrane colonizes SREBP-SCAP to the ER. When the level of intracellular cholesterol is too high, liver X receptors are activated, which inhibit enzymes related to cholesterol synthesis and reduce exogenous cholesterol uptake (102, 103). After organ transplantation, normal cholesterol homeostasis is disrupted and serum cholesterol levels are elevated (104, 105). Several human and mouse studies have shown that increased serum cholesterol disrupts cholesterol metabolic homeostasis and enhances TCR activity, Treg cells development, and T-cell proliferation (106, 107). An appropriate reduction in cholesterol leads to a decrease in the proliferation and function of T cells and the secretion of IL-10 and IL-12 (108). It also changes Th1 cells to Th2/Th3 cells and increases TGF- β 1 in circulation, the spleen and lesions (109). Previous studies have shown that the expression of FOXP3 in splenic Treg cells is upregulated under the influence of high cholesterol, but the proliferation of Treg cells does not inhibit the inflammation caused by T-cell activation. A likely reason is that the suppressive effect of Treg cells is limited by preactivated effector cells (106, 110, 111). However, depletion of FOXP3+ Tregs further aggravates hyperlipidemia and atherogenic inflammation (112). In contrast to previous findings, a recent study suggests that hypercholesterolemia mediates the inhibition of iTreg (inducible) cell differentiation *in vitro* by activating HIF-1 α to inhibit Foxp3 and target it for proteasomal degradation. Cholesterol triggers mtROS and inhibits degradation, which strongly induces HIF-1 α . This activation mode impairs the inhibitory activity of nTregs by inducing mitochondrial oxidative stress, damaging the mitochondrial structure, and inhibiting the differentiation of nTreg cells (113).

The protein levels of ABCG1 and ABCA1 are increased in cells in high-cholesterol environments, and cholesterol inhibits the degradation of these two proteins through the ubiquitin-proteasome pathway, which leads to their continuous increase in cellular content (114). These two proteins are involved in the reverse transport of intracellular cholesterol to the liver. The upregulation of the ABCG1 protein is suggested to be the cause of Treg cells suppression according to some studies. If the expression of cellular ABCG1 is too high, it leads to the downregulation of the p-STAT5/Foxp3 pathway in thymic Treg cells and the inhibition of Treg cells proliferation (115).

The functional activation of thymic TCRs and altered thymocyte differentiation, as well as Treg cells proliferation, have been observed in several studies with genotypes lacking the encoding ABCG1. This deficiency inhibits mTOR signaling and atherosclerosis (116, 117). Additionally, in the case of TCR stimulation, the loss of ABCG1 in CD4 T cells leads to excessive proliferation *in vitro*, which may cause a severe immune response (117). These results may explain why, in the context of hyperlipidemia, the activation of Treg cells was promoted but did not significantly suppress the inflammatory response.

LXR, a type α and β transcription factor, regulates T-cell proliferation and TCR activity by synthesizing oxysterols and activating the LXR transcriptional network to drive cholesterol efflux and reduce cholesterol influx and synthesis (101, 118). Current studies have shown that high cholesterol conditions increase the expression of LXR in T cells and that the activation of LXR leads to reverse cholesterol transport and inhibits the proliferation and cell cycle progression of T cells; additionally, LXR regulates T-cell activation through the ABCG1 pathway (101). In another study, overexpression of LXR α and LXR β led to a decrease in IL-17, which in turn led to a decrease in Th17. Specifically, LXR activated Srebp-1a and Srebp-1c, and srebp-1 activation affected Th17 differentiation through physical interactions with Ahr and suppressed the expression of related genes. In general, depletion of these cells effectively inhibited EAE development (119, 120). Other studies have shown that LXR activation can stimulate the transcription of the CD4⁺ T glycosphingolipid biosynthetic enzyme UGCG and enhance the lipid raft profile of the T plasma membrane, but additional related signaling pathways are also worth exploring (118). It has also been reported that LXR β activation inhibits GSK3 β phosphorylation, downregulates TCF-1 in CD4⁺ T cells, inhibits Tfh cells differentiation, and attenuates the GC response and antigen-specific IgG production (121).

Triglycerides can stimulate the proliferation of CD4 T cells, the expression of IL-17 and IFN- γ , and the differentiation of Th1 and Th17 cells *in vitro* (122). Furthermore, vLDL in hyperlipidemic patients may induce atypical Th1 pathway activation through the CD36 pathway (123).

3.2.2 Effects of hyperlipidemia on B cells

Previous studies have shown that diets high in cholesterol reduce B cell-mediated humoral immunity. Under high cholesterol conditions, 25-HC production is increased, and 25-HC can reduce the ability of B cells to differentiate into plasma cells by inhibiting SREBP2 gene expression and protein activation followed by entry into the Golgi apparatus to function (124). A cohort study revealed a strong inverse association between HDL cholesterol and IgD expression in B cells including naive B cells (125). Some studies have also shown that the expression of Tfr and Tfh cells is increased under a high cholesterol diet, whereas B cells are dependent on Trf to induce the expansion of Breg cells in the presence of Tfh cells (126). A high cholesterol diet leads to an increased risk of autoimmune diseases and the expansion of B cells. The loss of LXR α and LXR β expression in CD11c⁺ APC could facilitate this process by increasing Baff and April in the TNF family because of a high-cholesterol diet, which leads to increased B-cell proliferation (127). Additionally, high cholesterol disrupts the SDF-1: CXCR4 axis in BM and promotes B-cell mobilization (128). Under high-fat loading conditions, high-fat exposure and inflammatory stimuli induce CD53 *in vivo* in the liver and isolated primary hepatocytes. The transmembrane tetraspanins CD53/TSPAN25/MOX44 mediate B-cell development and lymphocyte migration to lymph nodes (129).

3.2.3 Effects of hyperlipidemia on NK cells

In mice fed a high-cholesterol diet, the number of NK cells is increased, and the expression of molecules related to NK cells activation receptors, cytokines and effector molecules that play cytotoxic roles is increased (130). Another study reported that lipid accumulation inhibited the killing of NK cells by reducing c-Myc/P300 and H3K27ac (131). In hyperlipidemic conditions, especially hypertriglyceridemia, the expression of CD36 on NK cells is increased and the PI3K-Akt-mTOR/FOXO1 signal transduction axis is downregulated. Low mTOR activity represents low glycolysis/FAS and reduced cell growth and function. Moreover, lipids express PD-L1, TGF- β 1, and NKG2D ligands to reduce NK activity (132).

3.2.4 Effects of hyperlipidemia on macrophages

Macrophages are important cells in hyperlipidemia and affect atherosclerosis. They are also sensitive to different lipids and differentially release inflammatory factors (133). Hyperlipidemia can lead to an increase in the M1 proinflammatory phenotype and a decrease in the M2 anti-inflammatory phenotype (134). Recent studies have further addressed the effects of hyperlipidemia on macrophages. One study suggested that excess intracellular cholesterol decreased ABCA1 expression and the upregulation of ABCA5 was the main cause of cholesterol efflux (135). Another study reported that hyperlipidemia can promote the restriction of PKC δ isoform activation in macrophages, which reduces its number and inflammatory response in the arterial wall (136). Among the coactivated isoforms, PKC δ activation has a proapoptotic effect on monocytes/macrophages (137). Hyperlipidemia promotes the activation of CD80⁺ macrophages, which further promotes the development of NKT cells by increasing CDd expression and accelerating early atherosclerosis (138). CD36 expression is increased in hyperlipidemic patients and can affect lipid metabolism in macrophages (136). One possible mechanism is that PCSK9 expression and CD36 expression increase inflammation (139), but further studies are needed to investigate the role and mechanism (140). Under hyperlipidemic conditions, the expression of macrophage-activating ApoE can be initiated by miR-146-a-5p vesicles, and miR-142-a-3p controls the transcription axis and thereby inhibits inflammation (141). Recent studies on macrophage immunity in hyperlipidemic heart failure have revealed that genes associated with lipid transport are downregulated and glycolysis and fatty acid synthesis are upregulated in myocardial resident macrophages in hyperlipidemic heart failure models. Bmp2, Cx3cl1 and Tlr6 were also found to be upregulated, which is consistent with the activation of the NF- κ B signaling cascade according to GSEA. In contrast to previous studies, Car3 was significantly downregulated in the cardiac macrophages of HFD-fed mice (142). Under high-lipid conditions, ER stress induces IRE1 α activation, inhibits M2 polarization and enhances M1 polarization (143). Furthermore, lipid overload is mediated through the endoplasmic reticulum stress pathway. Studies on the macrophage-cardiomyocyte regulatory axis reveal the potential effects of a variety of inflammatory cytokines secreted by macrophages on cardiomyocytes, especially on pathways such as hypertrophy, fibrosis, and autophagy (144).

3.2.5 Effect of hyperlipidemia on neutrophils

Hypercholesterolemia can induce an increase in neutrophils, which is possibly due to stimulation of granulopoiesis, enhanced bone marrow mobilization, and reduced peripheral clearance. Increased numbers of neutrophils adhere to arteries via the chemokines CCR1, CCR2, CCR5 and CXCR2 and cause early atherosclerotic lesions (145). CXCR2 in hyperlipidemic patients can aggravate brain damage caused by neutrophils after cerebral ischemia (146). One study showed that high-fat conditioning can stimulate splenic NOD1 and activate neutrophil recruitment, activation and function (147). Other studies have shown that high cholesterol disrupts the SDF-1: CXCR4 axis in the BM and accelerates neutrophil mobilization (128).

3.2.6 Effects of hyperlipidemia on dendritic cells

Hyperlipidemia can induce the expression of PD-L1, TGF- β 1 and NKG2D ligands in lipid-loaded DCs, which is related to NK cell activation (132). In addition, hyperlipidemia can increase ox-LDL and then activate retinoid X receptor α (RXR α) and IL-1 β to attenuate TSLP expression in cultured thymic epithelial cells (TECs). This activation results in the suppression of LAP and PD-L1 expression in DCs, which leads to defective Treg function (148). Under hyperlipidemic conditions, an increase in ox-LDL can lead to the activation of the TLR4/MyD88-NF- κ B signaling pathway in DCs and enhance their migration, maturation and secretion of inflammatory cytokines (149). Hypercholesterolemia causes rapid changes in DCs in the bone marrow, and unlike PDCs, the spleen and lymph node cDC2 subsets accumulate lipids. Although lipid-loaded cDC2s increase costimulatory molecule expression and cytokine production, their ability to initiate naive CD4 T cells is significantly impaired (150). Dyslipidemia inhibits Toll-like receptor (TLR)-induced DC activation and related inflammatory cytokine production, mainly because oxLDL upregulation inhibits TLR-induced IL-12p40 production in CD8 α - DC subsets. Inhibition of this subset results in impaired Th1 and enhanced Th2 responses (151). It has also been suggested that the enhancement of CD11c+ dendritic cells is beneficial to the function of CD4+ T cells under hyperlipidemic conditions (152).

3.3 Effects of amino acid metabolism on immunity

Amino acid metabolism can regulate T-cell function by regulating the mTOR signaling pathway. A variety of amino acids can regulate mTOR activity and selectively activate mTORC1 and mTORC2 to regulate T-cell differentiation. However, the general control nonsuppressor 2 (GCN2) signaling pathway regulates T-cell differentiation in a manner independent of amino acid activation (153, 154). The same amino acids can also affect the immune response through the PD-1/PD-L1 pathway. Glutathione can activate PD-L1 in tumor cells to inhibit T-cell activity, and the loss of PD-1 can induce immune tolerance (155, 156). In tryptophan metabolism, dendritic cells expressing IDO can increase the function of Treg cells through the tryptophan

metabolism pathway (157). Amino acid metabolism disorders are related to the occurrence of elevated uric acid. Studies have shown that exposure to bacterial amino acid metabolism disorders can lead to elevated uric acid, which in turn leads to gout. This metabolic disorder leads to immune abnormalities in intestinal T cells through the mTOR signaling pathway (158). Moreover, CD8-positive memory T cells can clear ammonia and promote memory cell development through urea and citrulline cycles (159). Studies on cancer and psoriasis have revealed that the activation of GLS1, which is the GLS isoform, enhances the IL17a promoter, promotes the proliferation of Th17 cells, and leads to immune inflammation and psoriasis. GLS loss is the cause of tumor immunosuppression (160, 161). Homoarginine strongly regulates the actin cytoskeleton of T cells by inhibiting myosin heavy chain 9 (Myh9) and thereby affects the function of CD4 T cells. Homoarginine also inhibits the proliferation of T cells and the migration of related chemokines (162). In macrophages, the metabolism of some amino acids also leads to the differentiation of M2 macrophages through the influence of mitochondria (163).

3.4 Effects of bile acids on immunity

3.4.1 Effects of bile acid metabolism on T cells

Bile acids play an important role in metabolic homeostasis. The Fxr, Shp, Lxr and Srebp1c genes, which are related to bile acid metabolism, are closely related to inflammation and immune hyperexcitability (164). 3-oxoLCA inhibits Th17 cell differentiation by direct physical binding to its key transcription factor, retinol-related orphan receptor γ t (ROR γ t), while isoalloLCA enhances Treg differentiation by producing mitochondrial reactive oxygen species (mitoROS), which leads to increased FoxP3 expression. IsoalloLCA-mediated Treg enhancement requires an intron-based FoxP3 enhancer, the conserved noncoding sequence 3 (CNS3), which is a distinct mode of action compared to previously identified Treg-enhancing metabolites that require CNS1 (165). Microbial metabolites in the gut can affect the systemic immune environment. Primary bile acids in the gut are metabolized by microorganisms into secondary bile acids. Deoxycholic acid (DCA) is the most abundant secondary bile acid in the human body and largely reduces the proportion of CD8 cytotoxic T cells and IFN- γ -producing cells. The mechanism involves DCA enhancing PMCA-mediated Ca efflux and reduces the intracellular Ca concentration, whereas low intracellular Ca inhibits NFAT2 signal transduction and inhibits CD8 T cell effector function (166). Dietary and microbial factors can affect the composition of the intestinal BA pool, affect the BA-VDR axis and regulate the expression of the transcription factor ROR γ in colonic FOXP3 regulatory T cells (Tregs). ROR γ + Tregs play a role in anti-inflammatory effects and inhibit excessive immune responses during the inflammatory response (167). GVHD also alters the BA pool and shows a decrease in most bile acids and an increase in ursodeoxycholic acid (UDCA) and intestinal Nr1h4 mRNA (encoding FXR) but a decrease in Gpbar1 (encoding TGR5). These changes affect the transcription and antigen presentation capacity of intestinal T cells. However, the effect on systemic T-cell expansion is not clear (168). T cell-induced inflammation reduces the

abundance of microbial-derived bile saline hydrolase (BSH) genes and increases the expression of FXR. This effect on the BA pool leads to an increase in bile acids, such as chenodeoxycholic acid (CDCA), which promote FXR receptor activation and a decrease in DCA that inhibits FXR activation. In this study, ursodeoxycholic acid (UDCA) was found to reduce FXR activation, effector T-cell activation and graft-versus-host disease (59, 169). UDCA and DCA disrupt the intracellular Ca concentration through mechanisms that inhibit Ca uptake by mitochondria and increase cytosolic Ca, which leads to STIM1 and ORAI1 uncoupling and impairing store-operated Ca⁺ entry. This process is essential for NFAT signaling and T-cell activation, which in turn decreases T-cell activation (170). Studies have shown that the loss of MDR1 (ABCB1) function in the inflammatory response indirectly leads to the upregulation of T_H17 cells, which secrete cytokines and aggravate the inflammatory response. Mdr1 functions in the presence of conjugated bile acid (CBA), which alleviates oxidative stress and maintains immune balance in T_H17 cells (171). Unconjugated glycocholic acid (LCA) can block the activation of T_H1 cells. The mechanism may involve the activation of the vitamin D receptor (VDR) after increasing the LCA concentration, after which the phosphorylation of ERK-1/2 is inhibited to reduce the activation of T_H1 cells (172). IsoalloLCA is an isoform of LCA that is transformed in intestinal bacteria. It can induce the mitochondrial production of mtROS and then induce NR4A1 recruitment to the Foxp3 gene promoter to stimulate Foxp3 gene expression and enhance iT_{reg} cell differentiation (173). TCA can inhibit the activity of CD3⁺CD8⁺ T cells and reduce their number both *in vitro* and *in vivo*, but the specific mechanism still needs to be explored (174). While 3-oxoLCA and isoLCA inhibited T_H17 cell differentiation *in vitro*, DCA and LCA inhibited T_H17 cell differentiation only *in vivo* (175).

3.4.2 Effects of bile acid metabolism on macrophages

SIRT5 is an important metabolic regulator. Recent studies have shown that the absence of SIRT5 leads to an increase in bile acids, mainly taurocholate (TCA), in hepatocytes and increased TCA leads to the M2-type transformation of macrophages (176). Chenodeoxycholic acid (CDCA) was determined to inhibit macrophage M2 transformation in an allograft model (177). In another study, the anti-inflammatory effect of ursodeoxycholic acid (UDCA) was partially mediated through FXR activation and NF- κ B inhibition, which led to macrophage transformation from M1 to M2 (178). During the process of macrophage activation, taurine cholate (TLC) downregulates several genes related to early macrophage activation and upregulates several genes that suppress immunity and stabilize macrophages. These findings indicate that TLC has multiple effects on macrophages and its effect on macrophages needs further study (179). DCA and CDCA can significantly increase the level of NLRP3 in macrophages. This activation is dependent on calcium influx into the mitochondria, which in turn promotes the transformation of macrophages to an inflammatory type. However, overexpression of FXR inhibited NLRP3 expression, which contradicts the activation of NLRP3 by FXR ligands (180). Moreover, previous studies have suggested that the activation of FXR can aggravate the immune response (59),

which suggests that the role of FXR needs to be further studied. It has also been reported that LCA, DCA, 3-oxoLCA and isoLCA can activate TGR5 and promote the transformation of M2 macrophages, which inhibits the activation of T_H17 cells and the inflammatory response (175).

3.4.3 Effects of bile acid metabolism on NK cells

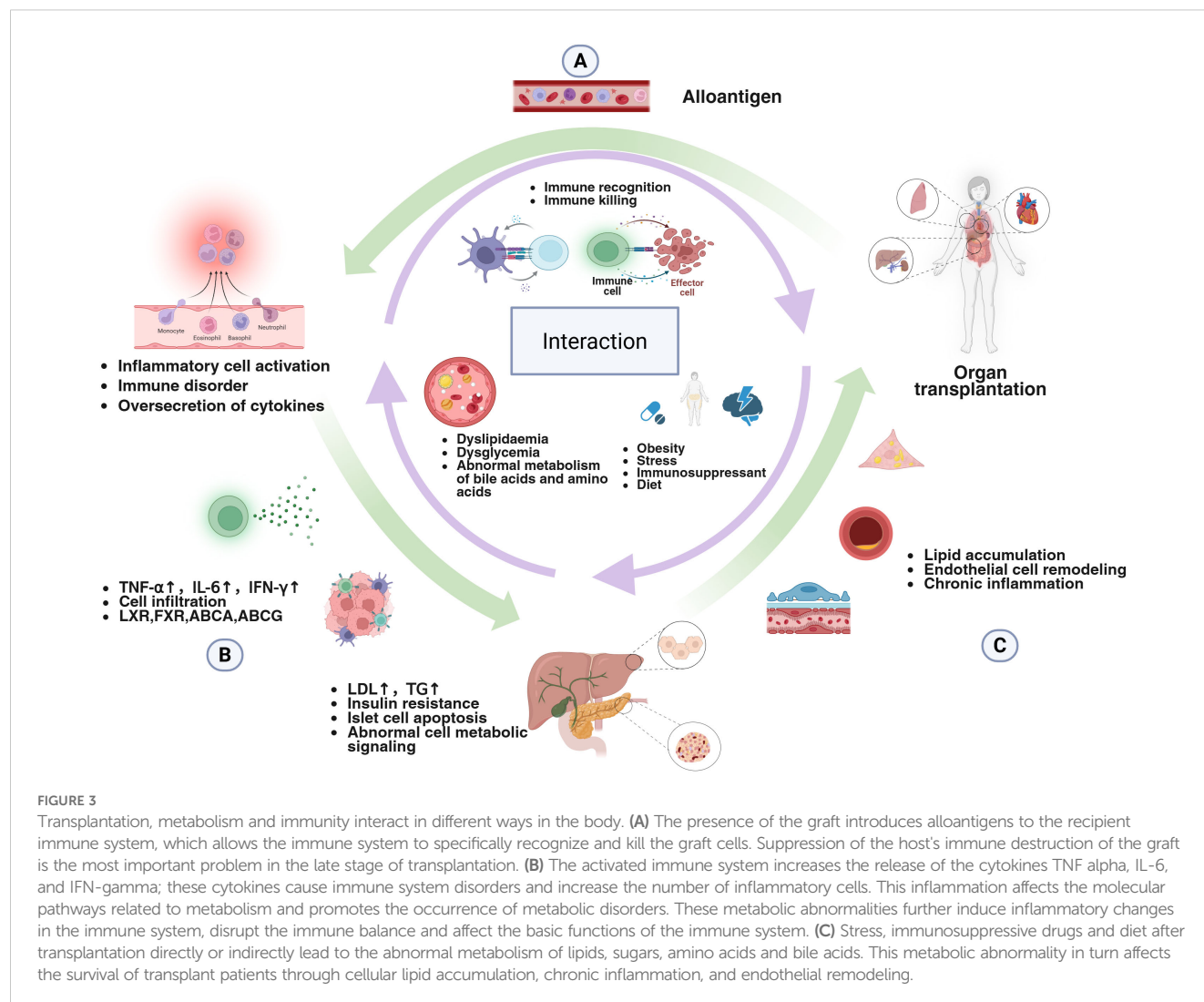
Taurocholic acid (TCA) reduces the activity and number of NK cells *in vivo* and *in vitro* and thereby inhibits their response to TNF- α ; however, the specific mechanism, which may be related to NKG2D expression, still deserves further study (174). The presence of TLC has been found to inhibit the gene expression of chemokines involved in NK cell migration, which also requires macrophage activation (179).

4 Effects of MetS on organ transplant rejection

After transplantation and due to a high-energy diet, that supplies needed macronutrients for recovery, side effects of immunosuppressive drugs, and reasons for reduced consumption, the incidence of obesity, nonalcoholic liver cirrhosis and metabolic disorders is significantly greater than that in the general population. Hyperlipemia, diabetes mellitus, and abnormal amino acid metabolism occur in most patients, and MetS is considered an important factor affecting the prognosis of transplant patients (53, 181, 182). Previous studies have demonstrated that patients developing MetS following cardiac, hepatic, or renal transplantation exhibit elevated inflammatory markers compared to non-MetS recipients. This systemic chronic inflammation, intrinsically linked to allograft rejection, mediates endothelial injury and exacerbates oxidative stress. Consequently, these pathophysiological alterations result in an elevated risk of cardiovascular events and accelerated allograft injury (Figure 3) (183–186).

4.1 Lipid metabolism and effects of transplantation

The most important effect of lipid metabolism after transplantation is an increase in cardiovascular disease (CVD) risk, and hyperlipidemia after transplantation is more likely to lead to coronary atherosclerosis (54). This particular vasculopathy is characterized by progressive narrowing of the graft vessel, which occurs after endothelial transplantation-related injury. Owing to the chronic immune response, the activation and interaction of related immune cell cascades leads to endothelial cell remodeling. Hyperlipidemia can also aggravate vascular stenosis by affecting endothelial cell function through a reduction in nitric oxide (NO) availability (187). The high incidence and serious consequences of CVD after liver transplantation make it a high concern among postoperative complications. Hyperlipidemia after a liver transplant is caused mainly by immunosuppressants (188). The relationship



between hyperlipidemia and atherosclerosis has been established by many studies (136, 145), and the current consensus is to protect the cardiovascular system and reduce CVD by lowering lipids (189). In a study of heart transplantation, the levels of triglycerides and ceramides in heart tissue (at the level of cardiomyocytes) increased after transplantation, and lipid accumulation in cardiomyocytes led to a reduction in both systolic and diastolic heart function (190).

Current studies on effects of hyperlipidemia on immune mechanisms have shown that high cholesterol promotes the proliferation of effector immune cells and enhances inflammation and rejection after transplantation (100, 106, 107, 128). Additionally, the pathways by which helper T cells and Treg cells control inflammation and proliferation are inhibited (113, 115, 117). This effect is achieved mainly through the activation or inhibition of LXR, ABCG, CD36, PCSK9 and other pathways under hyperlipidemic conditions (101, 115, 119, 123, 139, 140). Upon rejection, the induced lipid antigen-presenting CD1 protein and specific T cells that are predicted to recognize CD1b and CD1c proliferate vigorously and infiltrate the graft (191). Hyperlipidemia exacerbates allograft rejection by promoting macrophage polarization toward the pro-inflammatory M1 phenotype while

suppressing M2 differentiation, mediated through endoplasmic reticulum stress and downregulation of ABCA receptor expression (135, 139, 143). Concurrently, upregulated CD36 expression directly enhances macrophage cytotoxic activity, further amplifying rejection (139). Conversely, dendritic cell-mediated immune rejection is potentiated by elevated ox-LDL levels and increased CD11c+ dendritic cell populations, which act via both direct and indirect mechanisms (148, 152). This dendritic cell activation cascade drives B cell proliferation, thereby intensifying immune-mediated graft injury (127). This series of studies revealed that the influence of lipids on immune rejection is significant and that their related targets constitute future research directions for novel immunosuppressants.

4.2 Effects of glucose metabolism on transplantation

The incidence of diabetes after liver transplantation can be as high as 30%. Early hyperglycemia can be caused by stress due to surgery, postoperative infection, or steroid hormone use. Abnormal glucose

metabolism for more than 45 days is considered new-onset diabetes, which is related to the use of immunosuppressive agents and is also known to lead to CVD (188, 192). A clinical study revealed that posttransplant diabetes mellitus (PTDM) does not affect graft survival, whereas PTDM damages the kidney, reduces the renal function of the transplant recipient, increases blood lipids, and affects blood pressure, which affects the long-term survival of patients (55). Post-transplant diabetes abnormalities are also associated with CVD, and the presence of PTDM increases the relative risk of death from CVD in transplant patients by 1.5–3 times (193). Systemic insulin resistance, which is caused by immunosuppressive agents, occurs after transplantation (2). PTDM can lead to lipid accumulation in cardiomyocytes and then to the development of cardiomyopathy before coronary heart disease; however, this abnormal metabolism can be alleviated by metformin treatment (190). In addition, an increase in the level of macrophage-activated soluble CD163 (sCD163) was detected after transplantation. An increase in this marker implies disordered carbohydrate and lipid metabolism and increased inflammation, which is associated with the progression of MetS after transplantation and affects the survival of transplant patients (194). The occurrence of PTDM increases the infection rate of hospitalized patients, especially the CMV infection rate, which is significantly higher than that of transplant patients with stable blood glucose. Diabetes is a strong predictor of donor cardiac rejection and death, but other diabetes-related complications, such as microangiopathy after PTDM, are comparable to those of nontransplant diabetes (195). Current studies on diabetes and transplantation have shown that hyperglycemia not only promotes or inhibits immune cells in general but also has different effects on immune cells under different conditions. For example, hyperglycemia reduces the function of memory T cells under certain conditions (73), downregulates T-cell immunity (76), and both promotes and inhibits B cells (79, 81). Hyperglycemia exacerbates transplant rejection by augmenting cytokine production in T cells through upregulation of the MAPK signaling pathway (77). However, studies on macrophages have generally shown that hyperglycemia promotes macrophage transformation to the M1 phenotype, which is a proinflammatory response (82–84). Research pathways have focused mainly on PI3K/AKT, CD28, MAPK, STAT, NF- κ B and epigenetics. Mechanistically, hyperglycemia drives macrophage phenotypic switching via coordinated upregulation of Notch, SMYD3, MAPK, and IRF8 pathways coupled with downregulation of Arg1 and Mrc1 pathways. This transcriptional reprogramming enhances macrophage activation within the allograft microenvironment, potentiating their pro-inflammatory and cytotoxic functions to aggravate immune-mediated graft injury (74, 75, 82, 85, 91, 93, 98). Contact-related research on blood sugar and transplant rejection is also limited, and research on the immunosuppressive mechanism is not clear.

4.3 Effects of amino acid metabolism on transplantation

In a renal transplant study, the concentrations of BCAA (leucine, isoleucine, and valine) in patients who developed PTDM were consistently greater than those in posttransplant non-PTDM

subjects, and the concentrations of branch-chain amino acids and tyrosine in posttransplant subjects were greater than those in pretransplant subjects. The elevation of these amino acids was highly correlated with the development of posttransplant diabetes. This finding also indicates the possibility of insulin resistance but the related mechanism needs further study (196). Other studies have shown that the low amino acid content after transplantation is the cause of transplantation stress. The main reason is that the activation of ERK and AKT promotes the activation of mTORC1 and the consumption of amino acids in serum, whereas the inhibition of this pathway stabilizes stress after transplantation (197). Pretransplant sarcopenia predicts a decrease in amino acid levels after transplantation, which leads to a poor outcome after transplantation and suggests that protein and amino acid supplementation after transplantation is an important nutritional requirement (198–200).

The direct effect of amino acids on the immune system through the PD-1/PD-L1 pathway is also a major research direction of transplant rejection. Determining whether deficiency or an increase in related amino acids has a protective or destructive effect on transplant patients needs to be further studied. However, according to current studies, a stable serum amino acid balance still has a protective effect on transplantation (155–157, 163, 197).

4.4 Effects of bile acid metabolism on transplantation

Disorders in bile acid levels after transplantation are another important factor affecting survival time after organ transplantation. The inflammatory response after transplantation disrupts the balance of bile acids, increases the content of bile acids that promote immune rejection, and exacerbates the rejection of transplantation (59, 169). Prophylactic bile acid therapy was found to reduce the severity of acute graft-versus-host disease and inhibit intestinal cell apoptosis (168). In nonalcoholic steatohepatitis studies, dysregulation of bile acids was found to lead to hepatocyte apoptosis via DR5. Deoxyursodeoxycholic acid (NorUDCA) stabilizes this metabolic disorder and improves symptoms by downregulating the FXR receptor (201). The content of fecal bile acids after transplantation is related to the prognosis of patients, especially the risk of future infection. The type and content of bile acids can determine the mucosal immune capacity and resistance of pathogens to antibiotics (202).

In bile acid metabolism, the presence of secondary bile acids, such as 3-oxoLCA, DCA, and CDCA, reduces inflammation and rejection (165, 166). However, it is not known whether the resulting immunosuppression is specific and whether such use may aggravate posttransplant infections or further aggravate disorders of carbohydrate and lipid metabolism. However, the role of the related receptor FXR and its ligands in immunity is still controversial, which also makes bile acid metabolism a hot topic in the research of posttransplantation metabolism.

Current studies have shown that the main response caused by bile acid pool disorders in MetS patients after transplantation is to

promote immunity, and the treatment of bile acid disorders improves GVHD (59, 168, 169); however, studies in which ursodeoxycholic acid and NorUDCA are used to improve this disorder of bile acid metabolism still have limitations (59, 201). Disruption of the BA pool reduces BSH abundance and upregulates FXR expression, thereby promoting T cell expansion and driving a pro-rejection phenotypic shift (59, 169). Concurrently, loss of MDR1 function amplifies oxidative stress in effector T cells, exacerbating immune-mediated rejection (171). Furthermore, elevated levels of CDCA and DCA, coupled with reduced UDCA, suppress M2 macrophage polarization while promoting M1 polarization. This phenotypic reprogramming enhances macrophage-mediated pro-inflammatory activity, thereby aggravating allograft injury (178). In the future, more research is needed to stabilize bile acid disorders and reduce transplant rejection.

5 Management of MetS after transplantation

5.1 The impact of immunosuppressants on MetS

5.1.1 corticosteroids

Glucocorticoids exert the most profound metabolic impact in post-transplant patients, primarily through direct impairment of postprandial tissue glucose uptake, promotion of lipolysis, and elevation of serum triglycerides and free fatty acids. These mechanisms collectively exacerbate insulin resistance, leading to glucose intolerance and dyslipidemia (203). Furthermore, chronic glucocorticoid administration induces hypertension via fluid retention and endothelial dysfunction. Notably, while discontinuation mitigates metabolic disturbances, it concomitantly elevates rejection risk due to rebound immune activation (204).

5.1.2 Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin inhibitors (mTOR inhibitors) predominantly disrupt lipid metabolism in post-transplant patients by elevating circulating triglycerides and free fatty acids. This metabolic perturbation is mediated through impaired APOB100 degradation, leading to elevated triglyceride accumulation (205). Furthermore, mTOR inhibitor administration contributes to insulin resistance and diabetes pathogenesis, primarily mediated through dual mechanisms: interference with insulin signaling transduction pathways such as the IRS-1/PI3K/Akt cascade and suppression of pancreatic β -cell insulin secretory capacity (206–208).

5.1.3 Calcineurin inhibitors

Calcineurin inhibitors (CNIs), such as cyclosporine, predominantly disrupt lipid metabolism by inducing hyperlipidemia, marked by significant elevation of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides (209). In contrast, tacrolimus exhibits a higher diabetogenic propensity, primarily attributable to elevated FK506-

binding protein 12 (FKBP12) levels in pancreatic β -cells, which directly suppresses insulin secretion (210, 211).

5.1.4 Strategies for immunosuppressants adjustment

In the context of glucose dysregulation induced by immunosuppressive agents, glucocorticoid therapy is recognized to promote hyperglycemia; however, steroid withdrawal has not been shown to reduce the risk of PTDM (212). Studies indicate that maintenance therapy combining CNIs with glucocorticoids achieves an optimal balance between PTDM risk and acute rejection prevention. Notably, switching from tacrolimus to cyclosporine within CNI regimens significantly improves glycemic control without increasing acute rejection rates (213). Furthermore, concomitant use of mTOR inhibitors with CNIs does not elevate PTDM risk. mTOR inhibitor co-administration allows CNI dose reduction, thereby ameliorating glucose metabolism disturbances (214).

In transplant recipients exhibiting persistent hypercholesterolemia under CNI therapy, studies demonstrate that substituting cyclosporine with tacrolimus represents an effective therapeutic strategy (215). Hyperlipidemia induced by mTOR inhibitor administration is highly prevalent. If lipid levels remain suboptimal despite lipid-lowering agents, dose reduction of mTOR inhibitors and/or substitution with CNIs or alternative immunosuppressants is clinically warranted (188).

5.2 Diet and medication management

The evaluation of different risk factors in patients with MetS should achieve different goals with different strategies (216). Presently, the treatment of MetS is based on two main approaches as follows: drug management and diet management. Traditional dietary management models mainly include Med DIET, DASH, vegetarian, low-fat, low-carbohydrate and other models, and exercise can reduce the incidence of MetS after transplantation (Table 2). This comprehensive management helps maintain metabolic stability in patients with MetS (213, 217). The second type of drug management involves the use of statins, insulin, and oral antidiabetic drugs to control MetS (Table 3) (218).

5.2.1 Glycemic management

PTDM requires individualized therapy with a combination of diet, insulin, and oral hypoglycemic agents. Metformin stands out as an oral drug because it does not bind to proteins and remains stable in terms of excretion. When GLP-1 receptor agonists are used, their interaction with immunosuppressive agents should be considered. Studies have shown that the use of vildagliptin is safer after transplantation and that GLP-1 inhibitors are more suitable for obese patients. Insulin is more suitable for oral drugs when blood glucose cannot be controlled (53, 185, 213). The replacement of immunosuppressive agents is not the first choice for PTDM. Current studies have shown that the effect of replacing immunosuppressive agents is limited, and more long-term and comprehensive studies are needed. This therapy should be considered only for severe drug-induced PTDM reactions (213).

TABLE 2 Dietary management of MetS.

Dietary patterns	Specific measures	Expected Results	References
Mediterranean Diet	• 35%-45% from fat, mainly unsaturated fatty acids; 35%-45% water and 15%-18% protein	• Reduce the incidence of cardiovascular disease and T2DM; reduce the blood pressure	(217, 222)
The DASH Diet	• 27% from fat, 55% from carbohydrate, 18% from protein, and some dietary cholesterol intake	• Reduce blood pressure, reduce the incidence of T2DM, and protect the heart	
Ketogenic Diet	• 20% to 30% from protein, <50% carbohydrate intake, and 30% to 70% fatty acid intake	• Decrease LDL and triglyceride; Increase HDL	
Plant-based Diet	• Eat plant-based foods and reduce animal-based foods	• Reduce blood pressure; reduce the incidence of coronary heart disease	

5.2.2 Management of hyperlipidemia

Statins have been shown to be effective and well tolerated, fibrates are effective but partially nephrotoxic, and ezetimibe has been shown to be safe in liver transplant recipients (185). However, statins are metabolized mostly by cytochrome P450-3A4 and so calcineurin inhibitors may be reduced. For persistent hyperlipidemia, a change in the use of immunosuppressive agents, such as cyclosporine, to tacrolimus or a reduction in the dose of mTOR should be considered (188, 219). Fish oil omega-3 fatty acids are partially effective in lowering blood lipids in isolated hypertriglyceridemia, and cholesterol levels should be monitored continuously during treatment with fish oil (185, 188).

5.2.3 Weight management

Weight management advocates a combination of diet and exercise rather than the use of drugs because weight-loss drugs can antagonize immunosuppressive agents in certain pathways. Bariatric surgery should be considered in special cases when it is difficult to reduce weight with diet and exercise. Overall, weight loss significantly reduces the mortality of transplant patients (53, 220).

TABLE 3 Pharmacologic management of MetS.

Type	Management style	Drugs	Advantages	Disadvantages	References
Blood glucose management after transplantation	Recommended level of control:HbA1c <7% (53 mmol/mol); no retinopathy or proteinuria;				
	Hypoglycemic Agents	Insulin	• Early control • Intravenous injection followed by subcutaneous injection		(185, 220, 223, 224)
		GLP-1	• More suitable for patients with hyperglycemia and obesity • helps to reduce body weight		
		Metformin	• Adverse effects were mild	• Caution in patients with renal failure	
		Sulfonylureas	• High safety	• drug interactions; • Cause low blood sugar	
		Glinides	• High safety		
		SGLT-2 inhibitors		• Causes hypovolemia • Increases the risk of genitourinary infections	
		Thiazolidinediones	• High safety		
	Replacement of immunosuppressive drugs	Cyclosporine replace Tacrolimus	• Reduce the incidence of PTDM	• Not as first-line treatment • It may affect immunosuppression and should only be considered in severe cases	
		mTOR inhibitor replace Tacrolimus			
Lipid management after transplantation	Recommended level of control: LDL-C<100 mg/dL and triglyceride concentration <250 mg/dL				
	Lipid-lowering Agents	Statins	• Well tolerated and effective	• Muscle toxicity and liver toxicity	(185, 219, 225, 226)

(Continued)

TABLE 3 Continued

Type	Management style	Drugs	Advantages	Disadvantages	References
		PCSK9 inhibitors	• Excellent lipid lowering effect	• Not as a first choice	
		Fish oil (omega-3 fatty acids)	• Safety and minimal drug interactions		
		Fibrates	• Elevate CNI levels • Use when triglycerides > 1000 mg/dL	• Nephrotoxicity	
		Ezetimibe	• High safety	• Weak lipid-lowering effect	
		Fibrous acid derivative	• Good tolerance	• Risk of rhabdomyolysis	
	Replacement of immunosuppressive drugs	Reduce Calcineurin inhibitors (CNI)	• Reduce the degree of lipid metabolism disorder caused by drugs		
		Reduce mTOR Inhibitors			
		Change cyclosporine into tacrolimus			
	Blood pressure management after transplantation	Recommended level of control: Blood pressure < 130/80 mmHg			
Blood Pressure Medications		Calcium channel blockers	• First-line drugs		(188)
		ACEI\ARB	• First-line drugs • Reduce proteinuria and cardiac afterload	• Exacerbating hyperkalemia	
		Beta-blockers	• Second-line Drugs		
		Loop diuretics	• Second-line Drugs		

5.3 Significance of MetS management

The benefits of effective management of MetS are unequivocal in both mitigating immune-mediated rejection and sustaining metabolic homeostasis. Maintaining circulating glucose, lipids, and amino acids within optimal ranges in transplant recipients reduces the proliferative and differentiation capacity of immune cells, stabilizes the immune microenvironment, and attenuates chronic inflammatory responses. Furthermore, these sustained beneficial effects may reduce the immunosuppressive burden and improve long-term quality of life by preventing metabolic toxicity-induced complications.

6 Conclusions and perspectives

The mechanisms underlying the relationship between metabolic syndrome (MetS) after transplantation and immune tolerance remain unclear, and its impact on immune system function has yet to be definitively confirmed by many studies. Current immunotherapy regimens have notable limitations. Low doses are often ineffective, while high doses may lead to complications such as tumors, infections, and MetS. As a result, the search continues for treatments that not only promote metabolic stability and reduce complications but also induce immune tolerance and improve long-term quality of life for

transplant recipients (221). One promising approach is the use of the new generation of lipid-lowering drugs, such as PCSK9 inhibitors, which have been shown to reduce blood lipids while simultaneously inhibiting immune rejection in heart transplantation (139). Additionally, PD-1 has been identified as a key player in both graft rejection and amino acid regulation (155, 156). Several new nanomaterials targeting metabolic pathways are being developed to address post-transplant complications, and innovative 3D printing materials are emerging as potential tools in the management of graft rejection (221). Furthermore, the role of microRNAs in MetS and graft rejection represents an exciting avenue for future research. Therapeutic strategies aimed at balancing bile acids and amino acids to alleviate systemic stress are still under investigation, and their potential applications could offer significant benefits for transplant patients in the future.

Author contributions

ZT: Validation, Writing – original draft, Writing – review & editing. ZL: Validation, Writing – review & editing. ZZ: Supervision, Validation, Writing – original draft, Writing – review & editing. WY: Visualization, Writing – original draft. YH: Validation, Writing – original draft. XL: Visualization, Writing – review & editing. KZ: Validation, Writing – original draft. JW:

Project administration, Validation, Writing – original draft. JX: Project administration, Validation, Writing – review & editing. YZ: Project administration, Validation, Writing – original draft. YW: Project administration, Validation, Writing – original draft. XZ: Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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