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REVIEW

Can Fundus Fluorescein Angiography be Performed for Diabetic Patients on Oral Metformin?[△]

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Abstract Metformin is a kind of biguanide hypoglycemic agent that has been widely used in patients with diabetes mellitus. In clinical practice, whether metformin should be stopped before Fundus fluorescein angiography (FFA) remains largely unclear. Some endocrinologists suggest stop metformin before FFA. However, ophthalmologists do not always adopt this opinion in their practice. This situation may lead to disputes between physicians and patients. This article analyzed contrast-induced nephropathy(CIN) and the related contrast agent, as well as the adverse reactions of fluorescein angiography. It pointed out that the discrepancy may be caused by misunderstanding of contrast agents used in FFA. For angiography using iodine contrast agent, metformin must be stopped because of the increased possibility of CIN, while for FFA using fluorescein sodium, no CIN has been reported yet. Therefore, the authors believe FFA is safe for diabetic patients with oral metformin and it is unnecessary to stop metformin before the examination.

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METFORMIN is widely used in the treatment of type 2 diabetes mellitus due to its good effects in glucose-lowering, reducing the risk of cardiovascular complications and insulin resistance, and improving blood lipid metabolism. In clinical practice, some endocrinologists consider stopping met-

formin before Fundus fluorescein angiography (FFA). However, ophthalmologists do not always adopt this opinion in their practice. Such inconsistent conceptions may lead to disputes between physicians and patients. Therefore, this article discusses this discrepancy and clarify the safety of FFA in diabetic patients on oral metformin.

Metformin and contrast-induced nephropathy

Contrast agents have a wide range of applications in modern clinical practice. Angiography using contrast agents is often ordered for diabetic patients with the potential complication of vasculopathy. However, contrast agents may cause acute kidney damage, known as contrast-induced nephropathy (CIN),

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which has been reported as the leading cause of acute renal failure in hospitalized patients (11%).¹ CIN, which is mainly induced by iodinated contrast media (ICM), is an acute renal insufficiency occurred in patients with normal renal function, or a worsen of chronic renal insufficiency.² Although ICM is relatively safe, adverse events occurs from time to time. The typical clinical manifestation of CIN is non-oliguria acute renal damage, which generally occurs within 1 or 2 days after contrast application. The kidney function damage peaks at 3 to 5 days, and in some patients, it may return to normal at 7 to 10 days. In 25%-30% patients, it may progress to chronic renal failure, which requires renal replacement therapy.³ The incidence of CIN is higher in diabetic patients with vasculopathy, and much higher in those with renal failure (26%-50%).⁴ Therefore, diabetes mellitus is an important risk factor for CIN, particularly in patients with renal functional impairment.⁵

Besides diabetes mellitus, CIN was associated with some other risk factors including renal failure, multiple myeloma, circulating blood volume decrease (cirrhosis, nephrotic syndrome and dehydration), and nephrotoxic drugs.^{6,7} The reasons for CIN may be the changes in renal hemodynamics, hypoxia of renal medulla, and cytotoxicity.⁸ Renal hypoxia, combined with the generation of reactive oxygen species (ROS), plays a central role in the pathogenesis of CIN.⁵ These factors together result in severe injury of kidney function. There is no effective treatment for CIN at present. However, some measures can reduce the incidence of CIN, including nephrotoxic drug withdrawal, use of preventive medicine, and hydration therapy.⁹ Among these measures, the most important is drug withdrawal, including withdrawal from metformin, which may damage kidney function.

Metformin is one of the commonly used oral hypoglycemic drugs in patients with diabetes mellitus. It is the first-line drug in type 2 diabetes mellitus according to the Guidelines of Diabetes Prevention by the Diabetes Association of Europe and United States. It is also included in the first-line drugs of obesity-related diabetes in China. Metformin cannot be metabolized in the body, and is unable to bind with plasma protein. It is mainly filtered through the kidney in the form of prototype. Its mean plasma clearance half-life is about 4-6 hours and the half-life extends in patients with a decreased glomerular filtration rate.¹⁰

Since Metformin is mainly excreted in form of prototype by the kidneys, its excretion is blocked and it accumulates in the body when using contrast agents. This accumulation can damage kidney function, which will lead to a huge accumulation of metformin in the body, and could finally induce CIN. Furthermore, metformin increases the

production of lactic acid and prevents its metabolism. It increases the level of lactate and even induces lactic acidosis, which in turn aggravates the damage to kidney function, and proceeds to form a vicious circle subsequently. In addition, studies showed that patients with diabetes mellitus were more likely to suffer from CIN.⁷ Therefore, CIN prevention guides suggest that metformin should be stopped before and after angiography.¹¹

FFA and Diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of blindness in patients with diabetes mellitus. Early detection and treatment can greatly reduce the blindness rate.¹² FFA is one of the regular examinations in the diagnosis of DR,¹³ because it can detect early damages of the ocular fundus, such as fluorescein leakage, telangiectasia, and microaneurysms, that may not be detected by ophthalmoscopy. It can also accurately demonstrate the characteristics, size and location of the lesions, and guide laser treatment. Hence, FFA is an irreplaceable tool for the diagnosis, staging, treatment, and prognostic evaluation of DR.¹⁴

A variety of vascular contrast agents are used in different kind of angiography. As reported by the literature, the contrast agents related to CIN were generally iodinated contrasts. The essential characteristics of iodine is that X-ray can not pass through it, therefore iodinated contrasts are helpful in visualizing blood vessels in X-ray films. Iodinated contrast may lead to renal toxicity that is mainly associated with high osmotic pressure.¹⁵ Whereas fluorescein sodium, a non-iodinated contrast agent that is widely used in FFA, has a different angiographic mechanism. It is a water-soluble organic molecule that does not cause high osmotic pressure. When it enters the body through intravenous infusion, about 60% of fluorescein sodium binds with plasma albumin and does not generate fluorescence; about 20% of fluorescein sodium is free in the blood and emits fluorescence when it is passing through the retinal vein and excited by blue light. The physical barriers in the body can avoid fluorescein leakage to the tissues. Fluorescein sodium in the body is not involved in metabolism. It is mainly excreted in urine through kidneys, with a small percentage excreted from bile through liver. It drains from the body within 24 hours.

The safety of FFA

As the contrast agent used in FFA, fluorescein sodium does not participate in metabolism, so its toxicity is relatively light. In addition, the body has a good tolerance to it. Studies with large-sample in different populations (including Chinese) have confirmed the safety of FFA (Table 1).

Table 1. Adverse reactions of FFA reported in the literature

Author of studies	Number of cases	Incidence in total (%)	Adverse reactions				
			Nausea or vomiting (%)	Itching or rash (%)	Dizziness or sweating (%)	Others ^a (%)	Severe adverse reactions ^b (%)
Kwan <i>et al</i> ¹⁶	11898	1.1	1.1	0.2	0.3	0.2	0
Karhunen <i>et al</i> ¹⁷	9909	7.26	5.9	0.5	0.6	0.26	0.03
Butner <i>et al</i> ¹⁸	5000	4.82	4.02	0.34	-	-	0
Kwiterovich <i>et al</i> ¹⁹	2789	4.8	4.1	0.5	-	0.2	0
Lira <i>et al</i> ²⁰	1500	9.24	8.18	1.06	-	-	0.3
Ma H <i>et al</i> ²¹	3565	2.50	1.18	0.67	-	0.56	0.8
Liu J <i>et al</i> ²²	2620	0.34	0.07	0.07	0.07	0.11	0
Wei GC <i>et al</i> ²³	1119	7.06	5.27	0.36	0.71	0.71	0

a: Including chest pain, difficult breathing, fainting, sneezing, hypoglycemia, dye leakage, cough, dizziness, sweating, palpitation, pale face and throat discomfort.

b: Including anaphylactic shock, bronchospasm, laryngeal edema, pulmonary edema, and myocardial infarction.

-: Not reported in the article.

Yannuzzi²⁴ analyzed the adverse reactions of 221,781 FFA procedures ordered by 2,434 ophthalmologists. The study divided the adverse reactions of FFA into 4 classes according to the severity: 1) Mild: a short reaction without treatment, occurring quickly, full recovery without sequelae; 2) Moderate: a short reaction need some treatment, gradual recovery without sequelae; 3) Severe: a long reaction need strengthened treatment, different degrees of recovery with the involvement of respiratory system, heart, brain, or nervous system; 4) Death. The result showed that incidences of moderate adverse reaction, severe adverse reaction, and death were 1:63, 1:1,900, and 1:222,000, respectively.

Studies also demonstrated the safety of FFA in those with a history of drug allergy. Besides, it is also safe for some special populations including those with cardiac artery bypass grafts, cardiac pacemakers, old myocardial infarction, uremia, or cerebral infarction; those with mild reactions (nausea or vomiting) to the contrast agent at the previous examination; and those healthy people over 80 years old.²⁵

Therefore, based on the results from a large number of studies, fluorescein sodium used in FFA is by far a safe contrast agent with no direct damage to renal function. Furthermore, there has been no report about patients who use metformin experiencing serious adverse reactions during and after FFA examination.

CONCLUSION

The discrepancy on stopping metformin for diabetic patients to have FFA between some endocrinologists and ophthalmologists may be caused by the misunderstanding

of contrast agents used in FFA. For angiography using iodine contrast agent, metformin must be stopped because of the possibility of CIN; while for FFA using fluorescein sodium, no CINs has been reported as the adverse reaction due to the contrast agent. Therefore, we believe, FFA is safe for diabetic patients on oral metformin, and it is unnecessary to stop metformin before the examination.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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