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High Accumulation of Metformin in Colonic Tissue of Subjects With Diabetes or the Metabolic Syndrome

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Conflicts of interest
The authors disclose no conflicts.

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Dear Editors

The recognition that the hyperinsulinemic state is associated with the metabolic syndrome or type II diabetes mellitus is linked with increased colorectal cancer risk has led to studies of antidiabetes drugs to prevent cancer.[1] Metformin has multiple actions that contribute to its potential anticancer effects,[1] and has been associated with reduced cancer incidence and mortality in diabetic patients[2] and patients with colorectal cancer specifically.[3] In a recent double-blind, placebo-controlled, randomized phase III clinical trial in 151 patients, a low dose of 250 mg/d of metformin was associated with a decrease of approximately 40% in colorectal adenoma recurrence 1 year after initial polypectomy.[4]

Although the liver is recognized as the major site of metformin pharmacodynamics, the gut as an important site of action.[5] To date, confirmation that metformin can reach the colonic tissue and attain adequate levels to exert direct potential antitumor effects in humans is lacking. We performed a pilot study in 12 subjects with diabetes or the metabolic syndrome to compare metformin concentrations in plasma with colonic tissue according to colon site. The median metformin plasma concentration was 0.0025 mmol/L (range, 5×10^{-5} to 0.017). The median right and left colon tissue levels were 0.36 mmol/kg (range, 0.008–1.75) and 0.41 mmol/kg (range, 0.047–1.86), respectively. To explore whether the amount of metformin was simply coated on the mucosa or was absorbed into the tissue, weighted matched biopsies were washed before metformin quantification.

Metformin concentrations in washed tissue were 0.36 mmol/kg (range, 0.007–1.790) for the ascending colon and 0.35 mmol/kg (range, 0.041–1.89) for the descending colon, revealing no differences between concentrations in washed and unwashed specimens in the right and left colon. Plasma and tissue metformin concentrations according to colon site and washing procedure are shown in Figure 1*A*. The average metformin concentration in colonic tissues ranged from 0.026 to 1.82 mmol/kg (median, 0.37) and was closely related to the plasma concentrations (Figure 1*B*; r = 0.9063, $P = .0001$, Spearman).

Our findings show that the metformin absorption in colonic tissue is considerable, approximately 150-fold higher than in plasma. Moreover, metformin plasma and tissue concentrations were closely correlated, suggesting that the exchange between blood and

tissue occurs rapidly. Epidemiologic studies have consistently observed an association between metformin use in diabetic patients and decreased colon cancer incidence and mortality with therapeutic doses (1000–2250 mg/d),[2,3] corresponding with trough plasma levels of 0.03 to 0.045 mmol/L. A recent randomized phase III trial using a low dose of metformin (250 mg/d) in nondiabetics showed a 40% decrease in colorectal adenoma recurrence.[4] Interestingly, in a pilot study in nondiabetics from the same group, metformin use at 250 mg/d for 1 month did not reduce blood glucose, and had no effect on insulin resistance, plasma cholesterol, or plasma triglyceride levels, suggesting that the adenoma recurrence suppression occurred through a direct mechanism rather than the attenuation of insulin resistance or hyperlipidemia.[6] Pre-clinical models used much higher metformin exposures, which ranged between 1 and 50 mmol/L for in vitro and 0.006 to 0.150 mmol/L for in vivo studies, and led to effects that cannot be translated into clinically tolerable doses.[7] To date, a systematic evaluation of the pharmacokinetic properties of metformin and particularly its distribution in target tissues is needed. It is noteworthy that in mice the greatest accumulation of metformin is in the gastrointestinal tract, contributing to the anti-hyperglycemic effect by decreasing glucose absorption and increasing glucose metabolism to lactate.[8] Moreover, compared with plasma concentrations, the maximum concentrations in the small intestine in mice is 3- to 10-fold higher after oral administration and also after intravenous administration, indicating that accumulation in the intestine is a consequence of metformin distribution from the blood rather than an accumulation during the absorption process.[8] It has been demonstrated that left- and right-sided colon cancers exhibit different clinical and biological characteristics, including *RAS* and *BRAF* mutations, which are more common among colon cancers arising in the right side. Our analysis revealed that metformin concentrations in right-sided (0.36 mmol/kg) and left-sided cancers (0.41 mmol/kg) were comparable and substantially higher than those in plasma, consistent with a potential clinical effect on cancer prevention throughout the colon. The reason for this large accumulation is unknown. Because washing revealed no differences between washed and unwashed tissue, contamination owing to superficial adhesion can be excluded.

In conclusion, retention of metformin in the colon might represent a deep compartment for the drug. The levels found in the colonic tissues are in the range of a direct antitumor effect observed in in vivo preclinical models. A 2-by-2 randomized clinical trial of metformin and aspirin in colon cancer patients is underway to further elucidate independent and synergistic antitumor effects.

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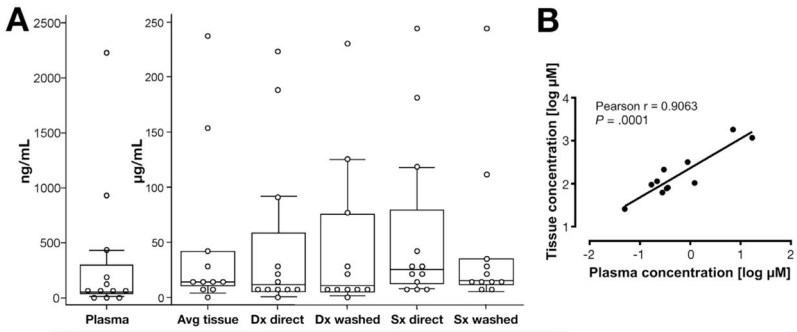

	Median	Range
Plasma (mmol/L)	0.0025	$5x10^{-5}$-0.017
Right colon unwashed (mmol/kg)	0.36	0.008-1.75
Right colon washed (mmol/kg)	0.36	0.007-1.79
Left colon unwashed (mmol/kg)	0.41	0.047-1.86
Left colon washed (mmol/kg)	0.35	0.041-1.89
Average tissue (mmol/kg)	0.37	0.026-1.82

Figure 1.

A, Plasma and tissue metformin concentrations according to colon site and washing procedure. R, right side; L, left side. *B*), Relationship of plasma and tissue concentrations of metformin.