

# What every dentist should know about metformin, diabetes, and cancer

Matthew R. Frykenberg ■ Abraham Schneider, DDS, PhD ■ Nasir Bashirelahi, PhD

Metformin has long been the drug of choice for treating patients with type 2 diabetes. Because of its effectiveness, safety profile, and affordability, it is used by millions of people worldwide. Emerging evidence indicates that metformin might also have antineoplastic effects in both diabetic and nondiabetic individuals. This article reviews studies that examine the

potential mechanisms of action underlying the anticancer properties of metformin and discusses the possible use of this antidiabetic biguanide in the chemoprevention and treatment of head and neck cancer.

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**M**etformin, commercially available as Glucophage (Bristol-Myers Squibb Company), Glumetza (Salix Pharmaceuticals, Inc.), Carbophage (Merck Serono), Riomet (Ranbaxy Laboratories, Inc.), and Fortamet (Shionogi Inc.), is the first-line drug for treating type 2 diabetes. Because it is affordable and has few adverse side effects, metformin is currently used worldwide by approximately 120 million people.<sup>1-3</sup> As an oral antihyperglycemic agent and insulin sensitizer, metformin functions primarily by reducing basal hepatic gluconeogenesis and secondarily by improving peripheral insulin sensitivity.<sup>4-6</sup> Metformin decreases the rate of glucose absorption from the intestine, but overall glucose absorption remains unaffected.<sup>6</sup> In addition to its beneficial control of blood glucose levels, metformin has been also associated with maintenance of current weight or weight loss; decreased levels of cholesterol, triglycerides, and low-density lipoprotein; increased levels of high-density lipoprotein; and reduced risk of cardiovascular diseases.<sup>1,5,6</sup>

Metformin is a biguanide originally derived from guanidine, the pharmacologically active component of the plant *Galega officinalis*.<sup>7</sup> *Galega officinalis*, also known as *French honeysuckle*, *French lilac*, *goat's rue*, *Italian fitch*, or *galega*, was brewed as a tea in medieval times for the treatment of maladies such as snakebite, plague, frequent urination, and worms.<sup>7</sup> Biguanides were derived from *Galega officinalis* in 1922 by Werner & Bell, and were discovered to be an antihyperglycemic agent in 1929 by Slotta & Tschesche.<sup>8,9</sup>

Because of the attention the discovery of insulin received, the biguanides escaped notice for several decades.<sup>10</sup> In the 1950s,

France approved the biguanides metformin, buformin, and phenformin for the treatment of type 2 diabetes.<sup>11</sup> In the 1970s, buformin and phenformin were banned due to harmful side effects in patients with renal, cardiovascular, and hepatic disorders, leaving metformin as the only hypoglycemic biguanide.<sup>11-14</sup> Metformin was cleared by the US Food and Drug Administration in 1994, and a commercial formulation was patented by Bristol-Myers Squibb Company in 1995.<sup>11,15,16</sup>

## Adverse effects of biguanides

Phenformin and buformin can cause lactic acidosis, which is why they were removed from the US market in the 1970s.<sup>11</sup> Metformin also carries the risk of lactic acidosis but at a rate of about 1/10 to 1/20 of that associated with phenformin.<sup>6</sup> The risk of lactic acidosis in patients taking metformin is estimated to be 0.03 per 1000 patient-years.<sup>6</sup> Lactic acidosis associated with metformin results in death in 50% of cases.<sup>6</sup>

In fewer than 5% of patients, metformin causes gastrointestinal symptoms such as nausea, vomiting, anorexia, abdominal pain, and diarrhea.<sup>6</sup> The incidence of these symptoms can be reduced by taking metformin with meals and initiating treatment with metformin at low doses.<sup>6</sup> Reportedly, 3% of patients develop a metallic taste sensation.<sup>6</sup> In 9% of patients, vitamin B<sub>12</sub> is reduced, though development of anemia is rare.<sup>6</sup>

## New uses for metformin

Despite metformin's long-time use for type 2 diabetes, new uses are coming to light. It has had an off-label use in the treatment of polycystic ovary syndrome since 2004, although 2 clinical studies found

that metformin was no more successful than placebo.<sup>17,18</sup> However, a 2012 study observed that, compared with clomiphene citrate, metformin can promote ovulation induction and pregnancy rate in women with polycystic ovary syndrome.<sup>19</sup> The effect of metformin combined with clomiphene citrate is better than that of either of the drugs used alone.<sup>19</sup>

It has also been suggested that metformin could control dementia and Parkinson disease and trigger the growth of nerve cells.<sup>20</sup> Preclinical studies in rodents revealed that metformin extends health span and life span in adult male mice and simulates some of the benefits of calorie restriction, such as improved physical performance.<sup>5</sup> Compelling observations gathered in the past decade have also indicated that metformin may trigger antineoplastic actions in a variety of tumor types.<sup>1,2,4,21-25</sup>

## Anticancer properties of metformin

### Evidence in the literature

One of the many consequences associated with type 2 diabetes is the increased risk of cancer. As interest in this link increased, various lines of research exposed additional ties between the 2 afflictions. In experimental preclinical studies, metformin has been shown to reduce tumor burden, delay tumor onset, and increase life span in healthy, nondiabetic mice.<sup>5</sup> In 2005, Evans et al reported that type 2 diabetes patients who were taking metformin appeared to be less likely to develop cancer.<sup>26</sup> Likewise, University of Alberta investigators reported in 2006 that mortality associated with cancer was less likely to

occur in patients with type 2 diabetes if they were taking metformin.<sup>27</sup> In a retrospective clinical study of 2592 breast cancer patients, including 157 with type 2 diabetes, Jiralerspong et al found that patients undergoing only chemotherapy had a recovery rate of 8%.<sup>28</sup> In contrast, in patients who were taking metformin in addition to chemotherapy, the recovery rate increased to 24%.<sup>28</sup> This promising evidence triggered the design and implementation of a number of randomized control trials in patients with a variety of cancer types.<sup>29</sup>

Metformin can potentially be used to treat a variety of cancers, including but not limited to skin, uterine, liver, pancreatic, colon, lung, ovarian, breast, and head and neck cancers.<sup>2,4,25</sup> In fact, metformin may help to prevent carcinogenesis in those patients with high risk of developing malignancies.<sup>2</sup> Anticancer drugs must go through years of trials and are expensive when made available to patients. Because metformin is relatively inexpensive, it can be afforded by many patients and by governments that would be unable to finance other drugs for their citizens. However, more studies are still needed before metformin can be repurposed for the oncologic setting.

### **Potential underlying mechanisms**

It has been proposed that the potential antineoplastic effects of metformin lie in a pathway activated by its antihyperglycemic function.<sup>21,22</sup> Metformin partially inhibits the mitochondrial respiratory chain complex I, resulting in decreased hepatic gluconeogenesis.<sup>3</sup> The subsequent metabolic stress causes an increase in the adenosine monophosphate–adenosine triphosphate ratio, which in turn activates the upstream tumor suppressor LKB1 protein kinase.<sup>4</sup> This results in activation of the adenosine 5′ monophosphate–activated protein kinase (AMPK) pathway, which signals cells to conserve energy in order to restore intracellular adenosine triphosphate levels.<sup>4</sup> Activation of the AMPK pathway leads to inhibition of the mammalian target of rapamycin (mTOR) pathway, an important regulator of metabolism and cell growth.<sup>4</sup> Because metabolism and cell growth are vital to cancer progression, metformin may be useful in the prevention and management of neoplasms.<sup>4</sup>

It should also be noted that cancer cells thrive in a milieu of high glucose and high insulin. Studies indicate that metformin might be indirectly inhibiting cancerous growth by lowering both glucose and insulin.<sup>21,22</sup>

### **Head and neck cancer**

Head and neck cancers, which largely comprise malignant lesions in the oral cavity and pharynx, are often fatal and are of great importance to oral healthcare providers. Annually, health professionals diagnose an estimated 600,000 cases of head and neck cancer worldwide, 47,560 of which occur in the United States.<sup>4</sup> Because it is often detected late, head and neck cancer has a 5-year survival rate of approximately 50%.<sup>4</sup>

Almost 75% of head and neck cancer cases are associated with the risk factors of tobacco and alcohol use.<sup>4</sup> Infection with human papillomavirus has recently emerged as another risk factor for head and neck cancer.<sup>4</sup> More than 85% of head and neck cancers are accounted for by head and neck squamous cell carcinoma (HNSCC).<sup>4</sup> HNSCC affects the oral cavity, salivary glands, paranasal sinuses, nasal cavity, pharynx, larynx, and the surrounding lymph nodes.<sup>4</sup> Even a slight elevation in the risk of cancer becomes a considerable social burden. It is therefore imperative to find novel approaches for cancer prevention.

Treatment plans for head and neck cancers usually involve either surgery or radiotherapy. Surgery results in the removal of noncancerous tissue in proximity to the tumor. Thus surgery is undesirable, because it can easily result in dysphagia, dysarthria, clotting disorders, and damage to sinuses, glands, and lymph nodes.<sup>4</sup>

Radiotherapy is preferable because it is more accurate and provides a greater probability of organ preservation. However, as Sikka et al wrote, “... resistance to radiation and recurrence after therapy are major drawbacks for patients with head and neck cancer and remains a point of emphasis for newer strategies of treatments in the future.”<sup>4</sup>

Metformin is thought to be an effective drug for arresting the development and growth of HNSCC because of the unregulated activity of the mTOR pathway. In a study of human-derived HNSCC cell lines, metformin selectively inhibited

tumor cell proliferation by disrupting mTOR signaling–driven translational control of a specific subset of messenger RNAs encoding cell cycle regulators.<sup>4,30</sup>

The effect of metformin occurs primarily in the basal layer of oral premalignant lesions, where proliferation occurs.<sup>2</sup> In a study of oral cancer induced by an oral-specific carcinogen in mice, Vitale-Cross et al reported, “metformin prevented the development of HNSCC by significantly reducing the size and number of carcinogen-induced oral tumoral lesions, and by preventing their spontaneous conversion to squamous cell carcinomas.”<sup>2</sup> The strong growth inhibition of HNSCC by metformin is not associated with any prominent cell death.<sup>4</sup> These results support the potential clinical use of metformin as a targeted chemopreventive agent in the control of HNSCC.

### **Conclusion**

The literature supports the need for clinical trials on, and possibly the eventual implementation of, the use of metformin in the oncologic setting. Because of its anticancer action, metformin has the potential to save lives, reduce costs, and prevent morbidity associated with the progression of neoplasms. This is relevant for dental treatment because there are promising indications that metformin could be effective in the treatment of HNSCC. Clinical trials studying this link should be initiated, and dentists should be aware of the possible future use of metformin for treatments other than type 2 diabetes.

### **Author information**

Mr. Frykenberg is a dental student, University of Maryland School of Dentistry, Baltimore, where Dr. Schneider is an associate professor and Dr. Bashirelahi is a professor of biochemistry.

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## Manufacturers

Bristol-Myers Squibb Company, New York, NY  
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