International Research Journal of Pharmacy and Pharmacology (ISSN 2251-0176) Vol. 3(8) pp. 112-115, December 2013
DOI: http:/dx.doi.org/10.14303/irjpp.2013.038
Available online http://www.interesjournals.org/IRJPP

Case Report

Metformin prevents progression of impaired fasting plasma glucose and CIN I cervical dysplasia: a case report and literature review

Dr S E Oriaifo*[1], Dr Nicholas Oriaifo[2], Prof E K I Omogbai[3], Dr J Egbeifo[4]

[*1]Dept. of Pharmacology, AAU, Ekpoma
[2]Dept. of Obstetrics and Gynaecology, ISTH, Irrua
[3]Dept. of Pharmacology Toxicology, UNIBEN. Benin-City
[4]HOD, Dept. of Obstetrics and Gynaecology, AAU and ISTH, Irrua

*Corresponding author`s email: stephenoriaifo@yahoo.com

Abstract

The epidemic of type 2 diabetes mellitus is unrelenting, at least, in the developing economies. A relationship has been noted between the insulin resistance or metabolic syndrome and cervical cancer; and a direct link may exist between glucose metabolism and cancer stem cells in tandem with recent reports that hyperinsulinaemia resulting from hyperglycaemia may promote carcinogenesis. Also, interference with energy metabolism may induce HPV suppression, a risk factor for cervical dysplasia and cancer. Metformin supplementation inhibited the ability of oncogenes to protect cancer cells from glucose deprivation-induced apoptosis. In this case report, metformin prevented the progression of impaired fasting plasma glucose to type 2 diabetes and arrested the progression of cervical intraepithelial neoplasia I (CIN I) in a 42-year old Nigerian female patient diagnosed with the metabolic syndrome and CIN I cervical dysplasia. Metformin's actions may be due to its activation of AMPK and also non-AMPK based actions such as downregulation of the oncogene, c-myc, the amplification of which is detected in preinvasive intraepithelial cervical cancer. Metformin's actions in prediabetes and CIN I deserves it being further explored.

Keywords: Metformin, Prediabetes, CIN I, HPV.

INTRODUCTION

Cervical cancer is among the most common cancers worldwide and the second most common cancer in women. It is associated with over 510,000 new cases and 288,000 deaths each year (Saslow et al., 2007; Xiao et al., 2012). The incidence in developed economies has been decreasing since the 1970s because of increasing use of preventive measures (www.mcdanielanddurrett.com/gynaecology). The Human Papilloma Virus (HPV) infection is thought to be necessary for the development of cervical cancer. Serotypes 16 and 18 of HPV are responsible for about 70% of all cervical cancers (Penaranda et al., 2013). The introduction of HPV vaccine is a major advance but current vaccines can prevent only 70% of cases (Saslow et al., 2007).

Pre-stages of cervical cancer are cervical intraepithelial neoplasia (CIN) I, CIN 2 and CIN 3. Diagnosis is done by cervical (Papanicolaou) smear and histological examination of biopsy specimens. In CIN I, biopsy may reveal atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL). For patients 25 years and older, follow-up is by a Pap test and HPV test in one year. If CIN I persists for two years, patients may undergo treatment. Present treatment for CIN I is

Table 1. Effect of Metformin on Progression of IFG and CIN I in a Pre-Diabetic

	At presentation	1yr	2yr	3yr
FPG (mg/dl)	112.50 ± 4.20	87.30 ± 5.00*	85.60 ± 3.00*	81.20 ± 5.00
BMI (kg/m^2)	32.50 ± 2.30	30.10 ± 4.00*	29.5 ± 5.20*	29.10 ± 6.00*
CINI	+ve	-ve	-ve	-ve
HPV	-ve	-ve	-ve	-ve

*Metformin caused significant reduction of body mass index (BMI), normalisation of fasting plasma glucose (*P < 0.05) and prevented progression of CIN I*

excisional or ablative therapy (www.uptodate.com). CIN I is no longer thought to be associated with an increased risk for CIN 3 (www.thedoctorschannel.com). Women diagnosed with CIN I are more likely to have HPV 16, which in turn increases the risk of CIN 3.

Differential diagnosis of CIN I includes benign conditions such as cervical infections, polyps and myxomas. It also includes iatrogenic states such as birth control pills and intra-uterine contraceptive devices (http://www.oncolex.no/en/Gynaecological.cancer).Symptoms of cervical intra-epithelial neoplasia may include abnormal bleeding between menses; during and after intercourse; or after menopause. There might be no symptoms and CIN I may be detected during routine screening.

There is now thought to be positive association between factors of the metabolic syndrome, such as hyperglycaemia, hypertriglyceridaemia and obesity, with cervical cancer. Findings suggest that the metabolic syndrome may play a role in virus-host interactions needed for infection with HPV to become persistent (Penaranda et al., 2013). Hyperinsulinaemia resulting from hyperglycaemia promotes carcinogenesis indirectly through increasing circulating free insulin-like growth factor-I (IGF-I) in tandem with the fact that a novel, direct link has been reported between glucose metabolism and cancer stem/initiating cells (Sato et al., 2012). Hyperglycaemia induces altered expression of angiogenesis associated molecules and upregulates expression of Il-6, Il-8, MCP-I, MMP-2 and MMP-9 (Chang and Yang, 2013). Decreased production of thrombospondin-I (TSP-I), a potent anti-angiogenic protein, by hyperglycaemia results in upregulation of angiogenesis in selected tissues (http://www.lerner.ccf.org).

5-adenosine monophosphate-activated kinase (AMPK) activation protects cells from oncogenic stimulation (Mihaylova and Shaw, 2011) and interference with energy metabolism by 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR) induces HPV suppression (Nafz et al., 2007). AMPK activators suppress cervical cancer cell growth (Kwan et al, 2013; Yung et al., 2013). Activation of AMPK provides a metabolic barrier to reprogramming somatic cells into stem cells by preventing the transcriptional activation of octamer-binding transcription factor 4 (Oct- 4), the master regulator of the pluripotent state (Vazquez-Martin et al., 2013). For example, generation of induced pluripotent stem cells (iPSCs) or tumor-propagating cells from somatic cells is blocked by metformin, an activator of AMPK. Metformin also targets cancer stem cells (Sato et al., 2012(b) and the cellular myelocytomatosis (c-myc) oncogene (Akinyeke et al, 2013) which is amplified in preinvasive intraepithelial cervical lesions (Aoyama et al., 1998; Golijow et al., 2001) and could cooperate in cell transformation and tumor progression. Infection with HPV 16 is tightly associated with c-myc amplification (Abba et al., 2004) and c-myc may be a target of HPV integration (Ferber et al., 2003).

The expression of histone deacetylase (HDACs 1 and 2) is increased in cervical dysplasia (Huang et al., 2005) and could also be a target of metformin (Duo et al., 2013).

Case report

A 42-year old Nigerian divorcee presented July, 2010 for routine pre-employment tests. Physical examination was normal except mild elevation of blood pressure (140/90 mm.Hg); impaired fasting plasma glucose (112 mg/dl); mildly elevated triglycerides (114 mg/dl); and increased body mass index (32.5 kg/m^2) which are features of the metabolic syndrome (Rao et al., 2004; Lily and Godwin, 2010). Papanicolaou smears from cervical specimens showed no cytological evidence of HPV infection but showed CIN I lesion with atypical squamous cells of undetermined significance. These tests were repeated yearly for three years.

Metformin was started for her at a dose of 500 mg thrice a day (Lily and Godwin, 2010; Fonseca, 2013; DeFronzo, 2009) Thereafter, plasma glucose levels became normal and cervical smears and biopsy specimens showed disappearance of CIN I lesions after one year (Table 1).

DISCUSSION

Results show that metformin halts the progression of impaired fasting plasma glucose (pre-diabetes) and CIN I pre-cancer lesions. Metformin, which activates AMP-activated protein kinase (AMPK), restores impaired glucose homeostasis and prevents the development of type 2 diabetes mellitus (Rao et al., 2004; Lily and Godwin, 2010). It decreases hepatic glucose production and increases fat oxidation, preventing chronic elevation of free fatty acid levels which is detrimental to maintenance of glucose homeostasis (Hsu et al., 2010; Ruderman et al., 1969). Metformin suppresses hepatic gluconeogenesis through induction of the NAD-dependent deacetylase sirtuin I (SIRTI) which promotes fatty acid oxidation (Sato et al., 2013; Purusotham et al, 2009); and the acetyltransferase general control of amino acid synthesis 5-like 2 (GCN5) (Caton et al., 2010). Acetylation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), the downstream target of AMPK, by GCN5 inhibits gluconeogenesis (Sakai et al., 2012). CBP-and p30-interacting transacting with glutamic-and aspartic acid-rich COOH terminal domain 2 (CITED 2) inhibits the acetylation of PGC-1α by blocking its interaction with GCN5 to increase gluconeogenic genes (Sakai et al., 2012). CITED 2 may be higher in subjects with pre-diabetes and type 2 diabetes mellitus.

Metformin has also been found associated with reduced cancer-related morbidity and mortality (Landman et al., 2010; Monami et al., 2010) by multi-faceted actions. The AMPK pathway seems dominant over the oncogenic signaling pathway in causing energetic deprivation and suppressing cell proliferation (Cheong et al., 2011). Activation of AMPK inhibits reprogramming of somatic cells into stem cells (Vazquez-Martin et al., 2013). Metformin kills cancer stem cells responsible for chemoresistance by cancer cells, inhibits cellular transformation and antagonizes epithelium-to-mesenshymal transformation (EMT) necessary for cancer spread. Metformin lowers threshold for stress-induced senescence and attenuates the anti-senescence effects of the Warburg-like aerobic ATP-generating hyperglycolytic metabotype required for self-renewal, immortality and proliferation of cancer stem cells (CSCs) (Del Barco et al., 2011). Metformin is also synthetically lethal with glucose withdrawal in cancer cells (Menandez et al., 2013).

Nestin expression, which correlates with the presence of cancer stem cells and aggressive growth and may be found in CIN I lesions (Sato et al, 2012(B), is inhibited by metformin (Sato et al, 2012) which may also inhibit cellular proliferation or induce apoptosis to reduce tumor bulk.

The observed reduction in cancer risk and mortality of diabetic patients chronically treated with the biguanide metformin (Monami et al., 2010) may represent a metronomic chemotherapy approach targeting the differential utilization of *de novo* one-carbon metabolism by pre-malignant and malignant cells. By functioning as a *bona fide* low-dose metronomic chemotherapeutic, the antifolate metformin may lead to tumor suppression by devascularising early tumor vessels and prevent systemic genomic damage (Corominas-Faja et al., 2012). Metformin-induced activation of the tumor suppressive ataxia telangiectasia mutated kinase (ATM)/AMPK axis is secondary to metformin-induced alteration of de novo nucleotide pool maintenance (Corominas-Faja et al., 2012).

The biguanide, metformin, has anti-angiogenic effects i*n vitro* and i*n vivo* (Soraya et al., 2012; Tan et al., 2009) and may also inhibit histone deacetylase (Duo et al., 2013) which may also help explain present results.

In conclusion, the pleitropic actions of metformin (http://apiidia.org) places it in good stead to prevent progression of impaired fasting plasma glucose and pre-cancer lesions of the uterine cervix, and deserves further exploration.

REFERENCES

Abba MC, Laguens RM, Dulout FN, Golijow CD (2004). The c-myc activation in cervical carcinoma and HPV infections. Mutat Res. 577(2): 151-8

Akinyeke T, Matsumara S, Wang X, Wu Y, Schalfer ED, Saxena A, Yan W, Logan SK, Li X (2013). Metformin targets c-myc oncogene to prevent prostate cancer. Carcinogenesis. doi: 10.1093(carcin)bgt.307

Aoyama C, Peters J, Senadheera S, Liu P, Shimada H (1998). Uterine cervical dysplasia and cancer: identification of c-myc status by quantitative polymerase chain reaction. Diagn. Mol. Pathol. 7(6): 324-30

Caton PW, Nayeni NK, Kieswich J, Khan NQ, Yaqoob MM, Corder R (2010). Metformin suppresses hepatic gluconeogenesis through induction of SIRTI and GCN5. J. Endocrinol. 205: 97-106

Chang S-C, Yang W-CV (2013). Hyperglycaemia induces altered expressions of angiogenesis associated molecules in the trophoblast. Evidence Based Complementary and Alternative Medicine. Retrieved From: http://dx.doi.org/10.1155/2013

Cheong JH, Park ES, Liang J, Dennison JB, Tsavachidou D, Nguyen-Charles C, Cheng ICW, Hall H, Zhang D, Lu Y, Ravoori M, Kundra V, Ajani J, Lee J-S, Hong W-K, Mills GB (2011). Dual inhibition of tumor energy pathway by 2-deoxyglucose and metformin is effective against a broad spectrum of preclinical cancer models. Mol. Cancer Ther. 10: 2350 doi: 10.1158/1535-7163/MCT-11-0497

Corominas-Faja B, Quirantes-Pine R, Oliveras-Ferraros C, Vazquez-Martin A, Cufi S, Martin-Castillo B, Micol V, Joven J, Segura-Carretero A, Menendez JA (2012). Metabolomic fingerprint reveals that metformin impairs one-carbon metabolism in a manner similar to the antifolate class of chemotherapy drugs. Aging. 4(7): 480-498

DeFronzo RA (2009). Banting lecture (From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus). Diabetes. 58: 773-795

Del Barco S, Vazquez-Martin A, Cufi S, Oliveras-Ferraros C, Bosch-Barrera J, Joven J, Martin-Castillo B, Menendez JA (2011). Metformin: multi-faceted protection against cancer. Oncotarget. 2(12): 896-917

Duo J, Ma Y, Wang G, Han X, Zhang C (2013). Metformin synergistically enhances antitumor activity of histone deacetylase inhibitor trichostatin against osteosarcoma cell line. DNA Cell Biol. 32(4): 156-64

Ferber MJ, Thorland EC, Brink AA, Rapp AK, Phillips LA, McGovern R, Gostout BS, Cheung TH, Chung TK, Fu WY, Smith D (2003). Preferential integration of human papillomavirus type 18 near the c-myc locus in cervical carcinoma. Oncogene. 22(46): 7233-42

Fonseca V (2013). Diabetes mellitus in the next decade: Novel pipeline medications to treat hyperglycaemia. Clinical Therapeutics. 35(5): 714-723

Golijow CD, Abba MC, Mouron SA, Gomez MA, Dulout FN (2001). C-myc gene amplification detected in preinvasive intraepithelial cervical lesions. Int. J. Gynecol. Cancer. 11(6): 462-5

Hsu I, Zuniga E, Bergman RN (2010). Pulsatile changes in free fatty acids augment hepatic glucose production and preserves peripheral glucose homeostasis. Am J Physiol Endocrinol Metab. 299(1): E131-6

Huang BH, Laban M, Leung CH, Lee L, Lee CK, Salto-Tellez M, Raju GC, Hooi SC (2005). Inhibition of histone deacetylase 2 increases apoptosis and p21Cip/WAF1 expression, independent of histone deacetylase 1. Cell Death Differ. 12(4): 395-404

Landman GWD, Kleefstra N, van Hateren KJJ, Groenier KH, Gans ROB, Bilo HJG (2010). Metformin associated with lower cancer mortality in type 2 diabetes. Diabetes Care. 33(2): 322-326

Lily M, Godwin M (2010). Treating prediabetes with metformin: Systematic review and meta-analysis. Can Fam Physician. 56(1): 18

Menendez JA, Oliveras-Ferraros C, Cufi S, Corominas-Faja B, Joven J, Martin Castillo B, Vazquez-Martin A (2013). Metformin is synthetically lethal with glucose withdrawal in cancer cells. Retrieved From: http://landesbioscience.com

Mihaylova MM, Shaw RJ (2011). The AMPK signaling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol. 13(9): 1016-23

Monami M, Colombi C, Balzi D, Dicembrini I, Giannini S, Melani C, Vitale V, Romano D, Barchielli A, Marchionni N, Rotella CM, Mannucci E (2010). Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care. doi: 10.2337/dc10-1287

Nafz J, De Castro Arce J, Fleig V, Patzelt A, Mazurek S, Rosl F (2007). Interference with energy metabolism by 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside induces HPV suppression in cervical carcinoma cells and apoptosis in the absence of LKBI. Biochem. J. 403(3): 501-10

Penaranda E, Shokar N, Ortiz M (2013). Relationship between metabolic syndrome and history of cervical cancer among a US National Population. ISRN Oncology. doi: 10.1155/2013/840964

Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X (2009). Hepatocyte-specific deletion of SIRT I alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metab. 9(4): 327-38

Rao RS, Disraeli P, Mcgregor T (2004). Impaired glucose tolerance and impaired fasting glucose. Am. Fam. Physician. 69(8): 1961-1968

Ruderman NB, Toews CJ, Shafer E (1969). Role of free fatty acids in glucose homeostasis. Arch. Intern. Med. 123(3): 299-313

Sakai M, Matsumoto M, Tujimura T, Yongsheng C, Noguchi T, Inagaki K, Inoue H, Hjooka T, Takazawa K, Kido Y, Yasuda K, Hiramatsu R, Matsuki Y, Kasuga M (2012). CITED 2 links hormonal signaling to PGC-1α acetylation in the regulation of gluconeogenesis. Nature Medicine. 18: 612-617

Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, Goldie SJ, Harper DM, Kinney W, Moscicki AB, Noller KL, Wheeler CM, Ades T, Andrews KS, Doroshenik MK, Khan KG, Schmidt C, Shafey O, Smith RA, Partridge EE (2007). American Cancer Society Guideline for human papillomavirus vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 57(1): 7-28

Sato A, Brace CS, Rensing N, Cliften P, Wozniak DF, Herzog ED, Yamada A (2013). SirtI extends life span and delays aging in mice through the regulation of NK2 homeobox I in the DMH and LH. Cell Metabolism. 18(3): 416-430

Sato A, Ishiwata T, Matsuda Y, Yamamoto T, Asakura H, Takeshita T, Naito Z (2012(B). Expression and role of nestin in human cervical intraepithelial neoplasia and cervical cancer. Int J Oncol. 41(2): 441-8

Sato A, Sunayama J, Okada M, Watanabe E, Seino S, Shibuya K, Suzuki K, Narita Y, Shibui S, Kayama T, Kitanaka C (2012). Glioma-initiating cell elimination by metformin activation of FOXO3 via AMPK. Stem Cells Translational Medicine. 1: 000-000

Soraya H, Esfahanian N, Shakiba Y, Ghazi-Khansari M, Nikbin B, Hafezzadeh H, Maleki Dizaji N, Garjani A (2002). Anti-angiogenic effects of metformin, an AMPK activator, on human umbilical vein endothelial cells and granulation tissue in rat. Iran J. Basic Med. Sci. 15(6): 1202-9

Tan BK, Adya R, Chen J, Farhatullah S, Heutling D, Mitchell D, Lehnert H, Randeva HS (2009). Metformin decreases angiogenesis via NF-kB and Erk1/2/Erk5 pathways by increasing the anti-angiogenic thrombospondin-1. Cardiovasc Res. 83(3): 566-574

Vazquez-Martin A, Vellon L, Quiros PM, Cufi S, de Galarreta ER, Oliveras-Ferraros C, Martin AG, Martin-Castillo B, Lopez-Otin C, Menendez JA (2013). Activation of AMP-Activated protein kinase (AMPK) provides a metabolic barrier to reprogramming somatic cells into stem cells. Retrieved From: http://www.landesbioscience.com

Xiao X, He Q, Lu C, Werle KD, Zhao R, Chen J, Davis BC, Cui R, Liang J, Xu Z-X (2012). Metformin impairs the growth of liver kinase BI-intact cervical cancer lines. Gynecol. Oncol. 127(1): 249-255

Yung MMH, Chan DW, Liu VWS, Yao K-M, Ngan HY-S (2013). Activation of AMPK inhibits cervical cancer cell growth through AKT/FOXO3a/FOXMI signaling cascade. BMC Cancer. Cell and molecular Biology. 13. Retrieved from: http://www.biomedcentral.com

How to cite this article: S E Oriaifo, Oriaifo N, Omogbai E K I, Egbeifo J (2013). Metformin prevents progression of impaired fasting plasma glucose and CIN I cervical dysplasia: a case report and literature review. Int. Res. J. Pharm. Pharmacol. 3(8):112-115