TRANSLATIONAL STUDY ON THE UTILITY OF METFORMIN TREATMENT IN CARDIOVASCULAR DISEASES

Mohapradeep Mohan, A.R.Cameron, G. Rena, C.C Lang
Division of Molecular & Clinical Medicine
University of Dundee, Scotland, UK DD1 9SY

PRESSING THE NEED FOR REPURPOSING OLD DRUGS

Developing a New Drug: Takes up to 15 years; Costly (over £2 Billion); Low success rate (< 8%); Risky

- Drug repurposing builds on previous research and development and can bypass many of the challenges and hurdles of conventional drug development process.
 - ✓ Less expensive (£250 million)
 - ✓ Less risky with high success rates.
 - ✓ Less time consuming (3-8 years) .

METFORMIN : OLD DRUG WITH NEW TRICKS

- Metformin is a cheap (2p per pill), generic and the most commonly prescribed drug for type 2 diabetes that has been used for over 50 years.
- Inflammation is understood to contribute towards many diseases including cardiovascular diseases and diabetes.
- Using a 'bench to bed side' approach, we studied the effect of inflammation and metformin use on prognosis in heart failure patients, and explored the anti-inflammatory effects of metformin using experimental and clinical studies.

METFORMIN IS ASSOCIATED WITH BETTER SURVIVAL

- Metformin use was associated with fewer deaths (36% relative risk reduction) in heart failure patients with diabetes, suggesting a possible cardio-protective effect of metformin.

INFLAMMATION IS HARMFUL IN CARDIAC PATIENTS

Chronic inflammation enhances the risk of death in heart failure patients.

- Neutrophil to lymphocyte Ratio (NLR); a marker of inflammation was associated with higher death rates in an observational study of 1660 patients with heart failure (1).

ANTI-INFLAMMATORY EFFECTS OF METFORMIN

A BENCH TO BEDSIDE STUDY

Animal Studies

- Metformin reduced expression of inflammatory markers interleukin-6, interleukin-1β, TNF-α and CXCL1/2 (2).

BIGDATA Analysis – Electronic Health Record Research

Summary of GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) Analyses, Comparing NLR in Metformin and Sulfonylurea Groups

Group Analyzed	12-mo Geometric Mean NLR Metformin vs Sulfonylurea % Difference (95% CI)	12-mo NLR<0 mo NLR Odds Ratio, Metformin vs Sulfonylurea (95% CI)
All subjects	-9% (2-15)	1.83 (1.22-2.75)
NLR above group median	-15% (5-23)	1.91 (1.02-3.59)

CI indicates confidence interval; and NLR, neutrophil to lymphocyte ratio.

- Metformin treatment reduced levels of inflammatory marker; NLR in diabetic patients (2) .

Randomised Controlled Clinical Trial Data

Change in cytokine	Covariate ΔBMI (P value)
Eotaxin/CCL11	0.004*
IL-2	0.006*
IL-4	0.008*
MDC/CCL22	0.004*
SDF1αβ/CXCL12	0.000*

- Metformin reduced the levels of inflammatory cytokines (2).
- Metformin improved exercise capacity in nondiabetic heart failure patients (3) .

SUMMARY / CONCLUSION

- Clinical evidence from our study suggest that a higher degree of inflammation bad in patients with heart disease and a potential survival benefit of metformin.
- Using a translational approach, we have shown that metformin exerts anti-inflammatory properties which may account for its unexplained cardio protective effects.
- Repurposing an existing drug such as metformin for CV disease has the potential of transforming lives globally.

References :

- (1) Mohan M et al., (2014) *Circulation*. 130:A15218
- (2) Cameron AR et al., (2016) *Circ.Res*. 119:652-665
- (3) Wong AKF et al., (2012) *European Journal of Heart Failure*. 14:1303-1310