METFORMIN: History and Clinical Evidence

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60 years of Metformin use

- 1957-2017
- 24,690 paper in ScienceDirect
Metformin: historical overview

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The discovery of metformin began with the synthesis of galegine-like compounds derived from *Gallega officinalis*, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries.

*Gallega officinalis* (also known as goat’s rue), a traditional herbal medicine in Europe, found to be rich in guanidine, which, in 1918, was shown to lower blood glucose.
Galega officinalis L

- Goat's rue, French lilac, Italian fitch, Spanish sainfoin or professor weed as a traditional medicine in medieval Europe.
- In Europe, wild G. officinalis was widely recognised as an animal galactagogue from which it gained its name ('Galega' being derived from the Greek for 'milk stimulant').
- The plant was introduced into North America in 1891 and is now classed as a noxious weed in many states of the USA.
- Chemical analyses of G. officinalis dating from the mid-1800s found the plant to be rich in guanidine and related compounds.
- The active ingredient in the French lilac is galegine or isoamylene guanidine.
Structure of guanidine and related compounds

Guanidine
1844–1861
Strecker

Mono-guanidine
1920
Galegine

Diguanidine

NH
H₂N–C–NH
Synthalin A

1878–1879
Rathke

NH
H₂N–C–NH–C–NH₂
Biguanide

1922
Wener & Bell

Metformin

NH
N–C–NH–C–NH₂
Phenformin

Biguanides

NH
N–C–NH–C–NH₂
Buformin

NH
N–C–NH–C–NH₂
Proguanil
John Hill recommended *Galega officinalis* to treat conditions of thirst and frequent urination (symptoms of diabetes).
1844–1861

- Identification and synthesis of guanidine (Strecker)
Synthesis of biguanide (Rathke)

\[
\begin{align*}
\text{NH} & \quad \text{NH} \\
\| & \quad \| \\
H_2N-C-NH-C-NH_2 & \\
\text{Biguanide}
\end{align*}
\]

Rathke, B (1879) Ueber die Einwirkung von Phenylsenföl auf Diphenylguanidin, Berichte der deutschen chemischen Gesellschaft, 12(1) 774-776
B. Rathke (1879) Ueber Biguanid, Berichte der deutschen chemischen Gesellschaft, 12(1) 776-784
- Guanidine lowers blood glucose in animals (Watanabe)

STUDIES IN THE METABOLIC CHANGES INDUCED BY ADMINISTRATION OF GUANIDINE BASES.

I. INFLUENCE OF INJECTED GUANIDINE HYDROCHLORIDE UPON BLOOD SUGAR CONTENT.

By C. K. Watanabe.

(From the Laboratory of Pathological Chemistry, School of Medicine, and the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven.)

(Received for publication, December 13, 1917.)

Rabbits were used in this investigation. Blood was usually drawn from the ear vein before and after the subcutaneous injection of a 10 per cent solution of guanidine hydrochloride. McDaniell’s (21) modification of the Lewis-Benedict method was used for the estimation of sugar in the blood and Fehling’s test for sugar in the urine. Duplicate determinations were done on the blood sugar to avoid technical errors. It was necessary to take some blood samples at night. In this case the specimen was immediately evaporated to dryness with the picric acid and determined colorimetrically the following morning. All specimens were evaporated to dryness with picric acid immediately on being drawn in order to avoid disappearance of sugar.

For the determination of total solids, the blood was drawn from the ear vein into a weighed crucible and dried to constant weight in an electric oven. About 2 cc. of blood were used for this determination and the sample for the blood sugar determination was taken at the same time. Comparison was made between normal rabbits and rabbits which had been injected with guanidine.

Hypoglycemia after the Injection of Guanidine Hydrochloride.

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Date</th>
<th>Weight</th>
<th>Guanidine per kilo at 9.10 a.m.</th>
<th>Blood sugar.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 a.m.</td>
<td>10 a.m.</td>
</tr>
<tr>
<td>7</td>
<td>June 30</td>
<td>2,220</td>
<td>0.101</td>
<td>0.100</td>
</tr>
<tr>
<td>8</td>
<td>July 2</td>
<td>2,240</td>
<td>0.121</td>
<td>0.112</td>
</tr>
</tbody>
</table>
Synthesis of dimethylbiguanide (Werner and Bell)

1926–1928

- Galegine and synthalin lower blood glucose in animals and humans

Metformin and other biguanides lower blood glucose in animals (Hesse and Taubmann; Slotta and Tschesche)

Use of guanidine derivatives to treat diabetes initially grows

Declines due to toxicity

Importantly, biguanides were deemed to be less toxic than mono- and diguanidines and, of the various methyl biguanides tested, metformin exerted the least toxicity

The real potential of these agents was underappreciated at the time

The biguanides were not developed for diabetes therapy and were forgotten during the following decade.

Additionally, because the availability of insulin.

1944-1947

- Guanidine-based antimalarial agent, *proguanil* (Paludrine),

- Lowers blood glucose in animals

1949-1950

- Dimethylbiguanide (flumamine) tested as potential antimalarial agent and used to treat influenza in Philippines.
- During clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose.
- It found to potentially lower blood glucose (Garcia)

Rediscovery via malaria and influenza

- A third strand in the history of metformin is the independent development of a guanidine-based antimalarial agent **proguanil** (Paludrine) in the mid 1940s.
- This drug was reported to cause a lowering of blood glucose in animal studies.
- In a search for other guanidine-based antimalarials, **proguanil** was modified to **metformin**, and tests for antimalarial activity by Eusebio Garcia in the Philippines, in 1949, found metformin to be helpful in treating a local influenza outbreak.
- This gave rise to the use of metformin hydrochloride as an anti-influenza agent called **flumamine**, and a tendency for metformin to lower blood glucose in some of the influenza patients was duly noted.
Jan Aron encourages Jean Sterne and Denise Duval to study guanidine-based glucose-lowering agents.
Jean Sterne publishes use of metformin to treat diabetes

Jean Sterne (1909-1997)

- Sterne suggested the name ‘glucophage’ (meaning glucose eater), which was adopted by Aron to market metformin, and Sterne played a prominent role in ongoing research and physician education to assist the introduction of metformin into clinical practice in Europe.
1957-1959

- Phenformin and buformin reported as treatments for diabetes

## Comparisons between metformin vs phenformin and buformin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Metformin</th>
<th>Phenformin</th>
<th>Buformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>More hydrophilic than phenformin or buformin</td>
<td>More lipophilic than metformin or buformin</td>
<td>Intermediate between metformin and phenformin</td>
</tr>
<tr>
<td>Log $P$ (octanol-water)</td>
<td>$-1.43$</td>
<td>$-0.83$</td>
<td>$-1.20$</td>
</tr>
<tr>
<td>Binding to mitochondrial membranes and inhibition of respiratory chain</td>
<td>Weaker</td>
<td>Stronger</td>
<td>Stronger</td>
</tr>
<tr>
<td>Location of anaerobic glycolysis</td>
<td>Mostly intestinal tissue exposed to high drug concentration</td>
<td>More generalised, including muscle</td>
<td>More generalised, including muscle</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Not metabolised, eliminated unchanged</td>
<td>About one-third hydroxylated by CYP2D6 (~9% Europids have CYP2D6 polymorphisms)</td>
<td>Almost all eliminated unchanged</td>
</tr>
<tr>
<td>Risk of lactic acidosis (events per 1000 patient-years)</td>
<td>$0.03–0.09$</td>
<td>$0.40–0.90$</td>
<td>$&gt; 0.10$</td>
</tr>
</tbody>
</table>
Metformin structure and pharmacokinetics

Planar molecule with single protonation between imino groups

Imino groups confer chelating properties, e.g. with copper

Non-polar methyl groups

Crystal structure stabilised with inter-molecular hydrogen bonds

Hydrophilic cationic base at physiological pH

Excreted unchanged (~20% filtered; ~80% secreted by kidneys)

- Bioavailability: ~50%
- $T_{max}$: ~2.5 h
- $C_{max}$: ~2 μg/ml
- $V_d$: ~100–300 l
- $T_{1/2}$: ~6–7 h

500–1000 mg
Metformin introduced to treat diabetes in the UK and other European countries
1958-1964

- **Sterne** and colleagues (especially **Azerad**) further evaluate metformin in individuals with diabetes.

- Their initial studies, mostly in insulin-treated individuals, included a mix of juvenile-onset and maturity-onset presentations of diabetes.

First large prospective comparator trial of metformin (Edinburgh, UK; notably Duncan, Clarke and Campbell)

1980–1977

- Phenformin and buformin withdrawn in most countries because of risk of lactic acidosis
- Lactate uptake by the liver is diminished with phenformin and buformin administration because lactate is a substrate for hepatic gluconeogenesis
The risk of lactic acidosis, especially with phenformin and buformin, was evident from the outset.

Controversy was fuelled when phenformin was withdrawn from the University Group Diabetes Program (UGDP) trial in the USA in 1971.

Phenformin was removed from the market in the USA in 1978.
Lactic Acidosis related to CYP2D6

- Ironically, soon after withdrawal of phenformin it was noted that about 9% of Europids have a mutation in the CYP2D6 gene, encoding the cytochrome P450 2D6 (CYP2D6) hydroxylation enzyme, causing a build-up of unmetabolised phenformin, leading to lactic acidosis.
- A problem that modern pharmacogenomics could deal with.
1980–1994

- Substantial new scientific and clinical evidence (e.g. Hermann, Noel, Wiernsperger and Bailey), strategic input by Lipha pharmaceuticals (e.g. Howlett, Meynaud, Daniel, Goodman) and discussions with the FDA (Reaven, DeFronzo, Bailey, Turner, Garber)

1994-1995

- Metformin approved (1994) and introduced (1995) in the USA
1995-1996

Key publications confirm favourable benefit:risk ratio of metformin in management of T2D

UKPDS (UK Prospective Diabetes Study) reports long-term metabolic effects of metformin and reduced cardiovascular risk with use.

2000-2002

- Extended-release formulation and fixed-dose combination drugs with metformin as the primary active ingredient are approved in the USA
Metformin became first-line pharmacological choice

Metformin has become the most prescribed glucose-lowering therapy world-wide and it is now included in the World Health Organization’s (WHO’s) essential medicines list.

<table>
<thead>
<tr>
<th>Year</th>
<th>Landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>Guanidine, a traditional herbal medicine (<em>Galega officinalis</em>) compound, lowers blood glucose in animal.</td>
</tr>
<tr>
<td>1920s</td>
<td>Guanidine derivatives, including metformin, were synthesised.</td>
</tr>
<tr>
<td>1930</td>
<td>some (not metformin) were used to treat diabetes.</td>
</tr>
<tr>
<td>1942</td>
<td>Metformin was rediscovered in the search for anti-malarial agents. During clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose.</td>
</tr>
<tr>
<td>1957</td>
<td>Jean Sterne (French physycian), who first reported the use of metformin to treat diabetes.</td>
</tr>
<tr>
<td>1995</td>
<td>Metformin was introduced into the USA.</td>
</tr>
<tr>
<td>1998</td>
<td>Long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS)</td>
</tr>
</tbody>
</table>
Mechanism of Action

- Metformin is also frequently described as an insulin-sensitizer, leading to reduction in insulin resistance and a significant decrease in plasma fasting insulin levels.

- The improvement in insulin sensitivity by metformin could be ascribed to its positive effects on insulin receptor expression and tyrosine kinase activity.

The mitochondrial respiratory chain complex 1 is the primary target of metformin.
Potential molecular mechanisms of the action of metformin on hepatic gluconeogenesis
Efficacy of Metformin

Clinical use of metformin in the treatment of type 2 diabetes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Monotherapy or in combination with other glucose-lowering agents including insulin in type 2 diabetes patients inadequately controlled by diet, exercise, and health education</td>
</tr>
<tr>
<td>Dosage forms</td>
<td>500, 850 and 1000 mg standard (IR) tablets (taken with meals); 500, 750 and 1000 mg XR tablets (mostly taken with evening meal); 500 mg/5 ml liquid formulation; 500 mg powder sachets</td>
</tr>
<tr>
<td>Titration</td>
<td>Increase dose slowly; monitor glycaemic control; maximal dose is 2550 or 3000 mg/day, depending on country (2000 mg/day in children)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Renal and hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; temporarily discontinue during use of i.v. radiographic contrast agents; pregnancy (although safe use is demonstrated in several studies)</td>
</tr>
<tr>
<td></td>
<td>N.B. Some guidelines have relaxed the renal contraindication and suggest: reduce metformin dose in renal impairment if eGFR &lt;60 ml/min/1.73m² (MDRD); avoid initiating metformin if eGFR &lt;45 ml/min/1.73m²; stop metformin if eGFR &lt;30 ml/min/1.73m²</td>
</tr>
<tr>
<td>Side effects</td>
<td>Gastrointestinal symptoms (may include diarrhoea) and metallic taste, likely to improve with dose reduction and re-titration; may impair absorption of vitamin B₁₂ and folic acid</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Risk of lactic acidosis in patients with a contraindication; hypoglycaemia can occur when taken in combination with another glucose-lowering drug or during alcohol abuse</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Check for contraindications; check plasma creatinine level or eGFR and haemoglobin periodically; possible interaction with cimetidine therapy</td>
</tr>
</tbody>
</table>
Pharmacodynamic effects of metformin in the treatment of type 2 diabetes

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Effect of metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>Improves glycaemic control in T2D; reduces progression of IGT and IFG to T2D</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Counters insulin resistance by several insulin-dependent and -independent actions that reduce hepatic glucose output, improve peripheral glucose disposal, increase intestinal anaerobic glucose metabolism and assist endothelial function</td>
</tr>
<tr>
<td>Hyperinsulinaemia</td>
<td>Reduces fasting hyperinsulinaemia</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Usually stabilises body weight; can facilitate reduction of excess adiposity</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>May modestly improve blood lipid profile in some hypertriacylglycerolaemic and hypercholesterolaemic individuals</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>No significant effect on blood pressure in most studies but blood pressure control may be improved in overweight individuals achieving weight loss</td>
</tr>
<tr>
<td>Proinflammatory state</td>
<td>May reduce CRP and some adipocytokines</td>
</tr>
<tr>
<td>Procoagulant state</td>
<td>Some antithrombotic activity, e.g. decrease in PAI-1, fibrinogen and platelet aggregation; improved capillary perfusion</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Reduced myocardial infarction and increased survival in T2D; reduced carotid intima-media thickness and reduced levels of adhesion molecules; other evidence for antiatherogenic activity, mostly from animal studies</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes
Other indications/Future direction

- Opportunities for its use in type 1 diabetes to improve glycaemic control and reduce required insulin dose.
- To slow or prevent progression of impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) (‘prediabetes’) to type 2 diabetes.
- Gestational diabetes.
- Various insulin-resistant states in which metformin has improved prognosis include polycystic ovary syndrome (PCOS), human immunodeficiency virus (HIV) -associated lipodystrophy, acanthosis nigricans and, possibly, dementia-type neurodegenerative disorders.
- Metformin might protect against certain cancers in individuals with type 2 diabetes.
- Advances in pharmacogenomics may better inform responsiveness to metformin and effects on the gut microbiome, and animal studies have intriguingly noted anti-ageing effects of metformin.
LESSONS

- There are endless generic lessons for medical research thinly disguised within the history of metformin.

- With hindsight, we are reminded that time spent searching early original literature can save valuable laboratory time, effort and money: vital clues can be concealed amidst throw-away observations in other areas of research.

- We are also reminded that the selection and interpretation of experimental models is fundamental, scrutiny within a drug class can reveal important differences, and we don’t have to know exactly how a drug works to reap benefit, but we do need to appreciate how to use it safely.
Upper row: Jean Sterne, Denise Duval, Jan Aron, Elie Azerad, Leslie Duncan, Basil Clarke, Ian Campbell, Leif Sparre Hermann, Harry Howlett, Michel Noel.


Missing: C. K. Watanabe, Emil Werner and James Bell, Erich Hesse and Gert Taubmann, Karl Slotta and Rudolf Tschesche, Eusebio Garcia.
THANK YOU