Biomarkers in the regulation of fertility: Specific Oct1 gene variants are associated with cardiovascular and death risk in metformin users

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Introduction

Metformin is widely used in fertility disorders of hyperandrogenemic women with insulin resistance e.g. in PCOS (Polycystic Ovary Syndrome) or in diabetes mellitus type 2 (T2DM). Polymorphisms in the Oct1 gene can alter the function or activity of organic cation transporter 1 (Oct1), thus changing metformin efficacy (Oct1 acting as its main transporter) as well as influencing the actions of Oct1 physiological substrates.

In the past, polymorphisms in Oct1 were associated with cardiovascular risk factors, thus they might contribute to cardiovascular risk development.

We aimed to determine the effect of intronic single nucleotide polymorphisms (SNPs) in the SLC22A1 gene on data of all-cause and cardiovascular death in the LURIC study, a large prospective cohort study of Caucasian individuals scheduled for coronary angiography to learn more about potential outcomes in metformin users and potentially establish pharmacogenetic biomarkers.

Methods

- An in silico analysis of 35 intronic SNPs in SLC22A1 in a GWAS cohort (LURIC) was performed.
- Out of the original LURIC cohort (n=3316), 3060 patients were available for subsequent analysis.
- Patients were grouped into diabetics, non-diabetics, metformin users and non-metformin users.
- Associations with all-cause and cardiovascular mortality as well as cardiovascular biomarkers were investigated.
- We identified 1219 T2DM patients, whereof 73 used metformin and 1146 were not on metformin therapy. 966 patient had no antidiabetic medication and 154 were sulfonylurea users.
- Cardiovascular mortality was assessed in all subgroups with the respective SLC22A1 rs3777392 genotypes using Cox proportional hazard models.

	Biomarkers							
	BMI	baseline insulin	baseline C-peptide	C-peptide 1h post glucose load	HOMA	HDL	LDL	TG
non diabetics	0.021	0.074	0.068	0.043	0.046	0.05	ns	ns
patients with T2DM	0.016	0.048	ns	ns	ns	ns	ns	0.007
non metformin users	0.009	0.049	ns	ns	ns	ns	ns	0.009
sulfonylurea users	ns	ns	ns	ns	ns	ns	ns	0.067
without medication	0.006	0.041	0.061	ns	ns	ns	ns	0.008
metformin users	ns	ns	ns	ns	ns	ns	ns	ns

BMI: body mass index; HOMA: homeostasis model assessment; HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglycerides; ns: not significant

Table 1: Associations with biomarkers: p-values for SNP rs3777392 per T allele in the investigated patient groups.

Results

Patients group	Statistical Parameters	All-cause death		Cardiovascular death	
		unadjusted	adjusted	unadjusted	adjusted
All patients	n number	3060	3008	3060	3008
	p-value	0.032	0.005	0.186	0.062
	HR	0.90	0.87	0.92	0.89
	CI	0.82-0.99	0.79-0.96	0.82-1.04	0.79-1.016
Patient without diabetes	n number	1820	1820	1820	1820
	p-value	0.180	0.376	0.660	0.975
	HR	0.85	0.90	0.94	1.00
	CI	0.68-1.08	0.71-1.14	0.70-1.26	0.75-1.35
Type 2 diabetics	n number	1219	1219	1219	1219
	p-value	0.977	0.975	0.758	0.776
	HR	1.00	1.00	0.86	0.97
	CI	0.83-1.21	0.83-1.22	0.76-1.22	0.76-1.23
Non-metformin users	n number	1146	1146	1146	1146
	p-value	0.796	0.922	0.457	0.673
	HR	0.97	1.01	0.91	0.95
	CI	0.80-1.18	0.83-1.23	0.71-1.17	0.73-1.22
without medication	n number	966	966	966	966
	p-value	0.642	0.563	0.663	0.724
	HR	1.05	1.07	0.94	0.95
	CI	0.85-1.30	0.86-1.33	0.71-1.24	0.71-1.26
Sulfonylurea users	n number	154	154	154	154
	p-value	0.250	0.120	0.515	0.356
	HR	0.74	0.62	0.82	0.71
	CI	0.44-1.24	0.34-1.13	0.45-1.49	0.35-1.46
Metformin users	n number	73	73	73	73
	p-value	0.147	0.698	0.047	0.066
	HR	1.65	1.32	2.08	8.67
	CI	0.84-3.25	0.32-5.37	1.01-4.28	0.86-87.05

HR: Hazard ratio, CI: Confidence interval

Table 2: Additive Cox proportional hazard models: p-values, hazard ratios and confidence intervals for SNP rs3777392 per T allele in the investigated patient groups.

Conclusions

- The C allele of SNP rs3777392 is associated with cardiovascular death risk in the LURIC cohort, Oct1 genotypes are significantly associated with various cardiovascular parameters in non diabetics and partly associated in T2DM.
- SLC22A1 genotypes modulate the pharmacokinetics and -dynamics of metformin with potential influences on the clinical response to metformin.
- A considerable percentage of T2DM or fertility patients might be “bad” or “non-responders” due to their Oct polymorphisms.
- Besides very positive effects in the majority of metformin users, some individuals may profit from a pre-treatment genotyping and careful monitoring.
- The development of diagnostic tests is highly warranted.
- Patients planned for metformin due to T2DM or fertility indications might then be tested prior to therapy start, in order to support personalized medicine approaches.

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