Salivary Heme Oxygenase-1: A Potential Biomarker of Idiopathic Parkinson Disease

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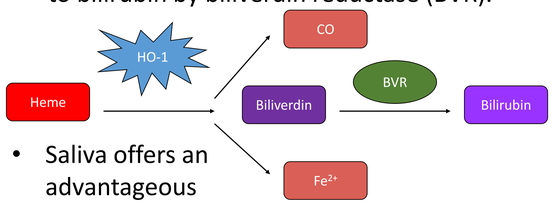
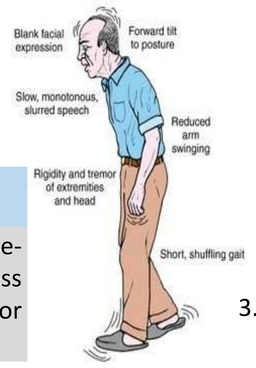
Background

- Heme oxygenase-1 (HO-1) has been implicated in the pathogenesis of idiopathic Parkinson disease (PD).[1]
- PD is a motor-neuro degenerative disorder characterized by tremor, rigidity, slowness of movement, postural instability, and in later stages, dementia.
- HO-1, an enzyme involved in the catalysis of heme, breaks heme down into biliverdin, ferrous ions (Fe^{2+}) and carbon monoxide (CO). Biliverdin is subsequently broken down to bilirubin by biliverdin reductase (BVR).



- Saliva offers an advantageous alternative to other biofluids and imaging modalities because its collection is non-invasive, inexpensive, and does not require advanced training of personnel.[2]



Aim

The main objective of this case-control study is to assess salivary HO-1 as a biomarker for idiopathic PD.

Methods

- 58 PD patients (mean age = 69.03±7.76 years) and 59 age and sex-matched non-PD controls (mean age = 65.05±7.81 years) were recruited for this study.
- All samples were collected from Jewish General Hospital (JGH) neurology, internal and family medicine clinics.
- All participants signed a consent form.
- Levels of HO-1 expression were assayed using enzyme-linked immunosorbent assay (ELISA) and Western blot analysis in whole, unstimulated saliva.

Results

1. HO-1 is detectable in saliva of patients with idiopathic PD and non-neurological controls. (**Figure 1**)

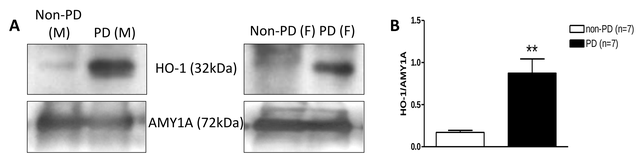


Figure 1

2. PD patients have significantly higher levels of HO-1 than controls (*P=0.03).
   - PD mean salivary logHO-1 concentration = 1.79 (95% confidence interval [CI]: 1.59-2.00); non-PD controls = 1.46 (95% CI: 1.25-1.66). (**Figure 2**)

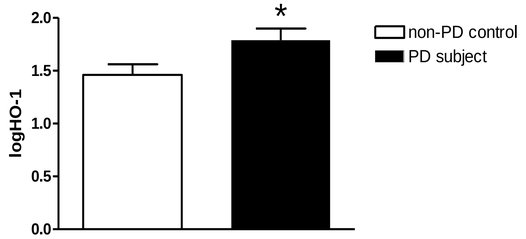


Figure 2

3. No significant statistical correlation of salivary HO-1 levels and common comorbidities were found. (**Table 1**)

Table 1. Comorbidities and salivary HO-1 levels

Disease	n	Mean logHO-1	95% CI	P-Value
Cardiovascular disorders	52	1.61	1.39-1.83	0.86
Non-cardiovascular disorders	65	1.64	1.44-1.84	
Cancer	12	1.83	1.38-2.67	0.35
Non cancer	105	1.60	1.45-1.76	
Diabetes	11	1.89	1.39-2.36	0.25
Non-diabetics	106	1.60	1.44-1.76	
Arthritis	30	1.74	1.45-2.04	0.36
No arthritis	87	1.58	1.45-1.75	
Thyroid problems	21	1.52	1.18-1.88	0.53
No thyroid problems	96	1.63	1.49-1.81	

Note: r values range from 0.02 – 0.13

4. Patients with Hoehn & Yahr (H & Y) stage 1 PD have significantly higher salivary HO-1 concentrations than non-PD controls and stages 2 and 3. (**Table 2**)

Table 2. Salivary logHO-1 levels and PD severity.

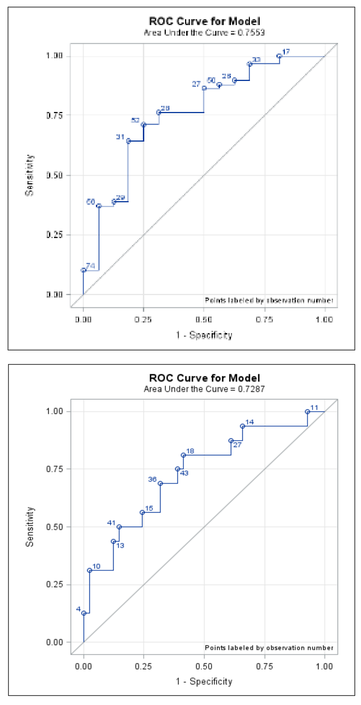
H&Y stage	n	Mean logHO-1	95% CI
0 (Control)	59	1.46	1.26-1.66
1	16	2.25	1.87-2.63
2	19	1.59	1.25-1.94
3	17	1.41	1.04-1.78

Note: $p^{0,1}$=0 .0004, $p^{1,2}$ = 0.01, $p^{1,3}$ = 0.002, $p^{0,2\&3}$>0.48

5. Levodopa equivalent daily dose (LEDD) was not associated with salivary HO-1 concentration (r = 0.0096, P = 0.95)

6. Satisfactory Receiver Operating Characteristic (ROC) curves were found between controls PD H & Y stage 1 (76%) (**Figure 3A**), and controls and PD cases [stages 1, 2 and 3] (73%). (**Figure 3B**)

Figure 3



Conclusions

- In saliva, idiopathic PD cases had significantly higher HO-1 concentrations than in control cases.
- Salivary HO-1 levels were not impacted by the comorbidities assessed.
- Salivary HO-1 was highest in stage 1 of the H & Y scale, suggesting that it is a potential biomarker of early idiopathic PD.
- PD medications did not affect salivary HO-1 concentrations.
- A commercially available ELISA kit is sensitive to measure salivary HO-1 levels accurately and reliably.

Future directions

- Validate salivary HO-1 as a biomarker for early idiopathic PD by increasing the sample size.
- Determine whether salivary HO-1 concentrations differentiate idiopathic PD from other degenerative and non-degenerative causes of Parkinsonism.

References

1. Schipper HM, Song W (2015) A Heme Oxygenase-1 Transducer Model of Degenerative and Developmental Brain Disorders. International journal of molecular sciences 16: 5400-5419.

2. Wang, J., Schipper, H. M., Velly, A. M., Mohit, S., & Gornitsky, M. (2015). Salivary biomarkers of oxidative stress: a critical review. Free Radical Biology and Medicine, 85: 95-104.

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